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FILE 'ENCOMPLIT2' ACCESS NOT AUTHORIZED
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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

INDEX 'ADISCTI, ADISINSIGHT, ADISNEWS, AGRICOLA, ANABSTR, ANTE, AQUALINE,
       AQUASCI, BIOENG, BIOSIS, BIOTECHABS, BIOTECHDS, BIOTECHNO, CABA, CAPLUS,
       CEABA-VTB, CIN, CONFSCI, CROPB, CROPU, DDFB, DDFU, DGENE, DISSABS, DRUGB,
       DRUGMONOG2, DRUGU, EMBAL, EMBASE, ...' ENTERED AT 18:11:39 ON 10 JUL 2006

92 FILES IN THE FILE LIST IN STNINDEX

Enter SET DETAIL ON to see search term postings or to view
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=> s (GLP-1 or  glucagon like peptide 1 or exendin2) (P)    (tandem or  repeat? or
cop? ) (P) (express? or produc?)  and (vector? or plasmid)
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=> s (GLP-1 or  glucagon like peptide 1 or exendin?) (P)    (tandem or  repeat? or
cop? ) (P) (express? or produc?)  and (vector? or plasmid)
          1*  FILE ADISNEWS
          0*  FILE ANTE
   6 FILES SEARCHED...
          0*  FILE AQUALINE
          0*  FILE BIOENG
          2   FILE BIOSIS
         11*  FILE BIOTECHABS
  11 FILES SEARCHED...
         11*  FILE BIOTECHDS
          1*  FILE BIOTECHNO
  13 FILES SEARCHED...
          6   FILE CAPLUS
          0*  FILE CEABA-VTB
          0*  FILE CIN
          1   FILE DGENE
  23 FILES SEARCHED...
          8   FILE EMBASE
          7*  FILE ESBIOBASE
  30 FILES SEARCHED...
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          0*  FILE FOREGE
          0*  FILE FROSTI
          0*  FILE FSTA
         11   FILE GENBANK
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          0*  FILE KOSMET
          0*  FILE NTIS
  45 FILES SEARCHED...
          0*  FILE NUTRACEUT
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  58 FILES SEARCHED...
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          0*  FILE WATER
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          0*  FILE INSPHYS
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=> D rank
F1          68   USPATFULL
F2          17   IFIPAT
F3          12   WPIDS
F4          12   WPINDEX
F5          11   GENBANK
F6          11*  BIOTECHABS
F7          11*  BIOTECHDS
F8           8   EMBASE
F9           7*  ESBIOBASE
F10          6   CAPLUS
F11          6   USPAT2
F12          3   INVESTEXT
F13          2   BIOSIS
F14          1   DGENE
F15          1   PHIN
F16          1*  ADISNEWS
F17          1*  BIOTECHNO


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                                                 ENTRY    SESSION
FULL ESTIMATED COST                              15.86      16.07

FILE 'IFIPAT' ENTERED AT 18:27:23 ON 10 JUL 2006
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FILE 'WPINDEX' ACCESS NOT AUTHORIZED

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L2           17 FILE IFIPAT
L3           12 FILE WPIDS
L4           11 FILE GENBANK
L5            8 FILE EMBASE
L6            6 FILE CAPLUS
L7            6 FILE USPAT2
L8            3 FILE INVESTEXT
L9            2 FILE BIOSIS
L10           1 FILE DGENE

TOTAL FOR ALL FILES
L11          66 L1

=> dup rem l11
DUPLICATE IS NOT AVAILABLE IN 'GENBANK, INVESTEXT, DGENE'.
ANSWERS FROM THESE FILES WILL BE CONSIDERED UNIQUE
PROCESSING COMPLETED FOR L11
L12           59 DUP REM L11 (7 DUPLICATES REMOVED)

=> d l12 1-59 ibib abs
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files.
REENTER DISPLAY FORMAT FOR ALL FILES (FILEDEFAULT):TI SO AU ABS ibib

L12  ANSWER 1 OF 59  IFIPAT  COPYRIGHT 2006 IFI on STN
TI    PHARMACOLOGICALLY ACTIVE PEPTIDE CONJUGATES HAVING A REDUCED TENDENCY
      TOWARDS ENZYMATIC HYDROLYSIS
INF   Larsen; Bjarne Due, Vanlose, DK
IN    Larsen Bjarne Due (DK)
AB    The invention is directed to a pharmacologically active peptide conjugate
      having a reduced tendency towards enzymatic cleavage comprising a
      pharmacologically active peptide sequence (X) and a stabilising petide
```

sequence (Z) of 4-20 amino acid residues covalently bound to X.

CLMN 47

AN 11114690 IFIPAT;IFIUDB;IFICDB

TITLE: PHARMACOLOGICALLY ACTIVE PEPTIDE CONJUGATES HAVING A REDUCED TENDENCY TOWARDS ENZYMATIC HYDROLYSIS

INVENTOR(S): Larsen; Bjarne Due, Vanlose, DK

PATENT ASSIGNEE(S): Unassigned

AGENT: CLARK & ELBING LLP, 101 FEDERAL STREET, BOSTON, MA, 02110, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2006063699	A1	20060323
APPLICATION INFORMATION:	US 2004-7772		20041207

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	US 1999-341590	19990712	PENDING

	NUMBER	DATE
PRIORITY APPLN. INFO.:	DK 1999-31798	19990309
FAMILY INFORMATION:	US 2006063699	20060323

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION

PARENT CASE DATA:

The present application is a continuation of co-pending application U.S. Ser. No. 09/341,590 as filed on Jul. 12, 1999, which application is a national phase entry under 35 USC (sec) 371 of PCT/DK99/00118 as filed on Mar. 9, 1999, which application claims the benefit of Danish application no. 0317/ 98 as filed on Mar. 9, 1998. The disclosures of the U.S. Ser. No. 09/341,590, PCT/DK99/00118, and Danish application no. 0317/ 98 are each incorporated herein by reference.

NUMBER OF CLAIMS: 47

L12 ANSWER 2 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN

TI INCREASING LIFE SPAN BY MODULATION OF SMEK

INF Dillin; Andrew, Del Mar, CA, US
Hunter; Tony, Del Mar, CA, US
Ma; Hui, San Diego, CA, US
Wolff; Suzanne C., Carlsbad, CA, US

IN Dillin Andrew; Hunter Tony; Ma Hui; Wolff Suzanne C

AB The Smek (Suppressor of mek null) gene is described and characterized. Smek acts in the stress response pathway of animals by binding to and enhancing the transcription of FOXO, thereby providing the link between the stress response pathway and the insulin/IGF-1 pathway. Given the link between both the stress response pathway and the insulin/IGF-1 pathway and longevity, Smek1 represents an essential target for modulation of life span and the stress response. Methods of increasing life span and stress tolerance by modulation of Smek activity are disclosed, as are screening methods for identifying compounds that modulate Smek activity. In addition, recombinant animals expressing the Smek gene that have a longer life span and enhanced stress tolerance, and methods of using the Smek genet to modulate both longevity and stress tolerance, are described.

CLMN 21 9 Figure(s).

FIG. 1: A) Sequence alignment of Smek orthologs from human, Drosophila, C. elegans and S. cerevisiae. B) Localization of Smek1 and Smek2 in the human genome. C) Domain structure of human Smek1

FIG. 2: Localization of Smek1 isoforms in 293T cells. A) Nuclear localization of GFP-tagged Smek1. B) Immunofluorescence staining of endogenous Smek1. C) Blocking of nuclear staining of Smek1 by antigen. D) Cytoplasmic localization of Smek1-S1GFP. E) Nuclear translocation of Smek1-S1-GFP after UV stimulation (180 J/m2, 6 hrs). F) Control GFP localization after same UV treatment as in E).

FIG. 3: A) Dose-dependent phosphorylation of Smek1 upon osmotic stress. 293T cells were stimulated with 0.3M and 0,6M sorbitol, respectively, lysed at different time points as indicated, followed by western blot analysis using Smek1 antibodies. B) Dose-dependent phosphorylation of Smek1 after UV treatment. HeLa cells were stimulated with different UV dosages and lysed after incubating for 1 hr at 37 degrees. C) Sustained phosphorylation of Smek1 in response to UV stress. 293T cells were treated with UV (180 J/m2), and cell lysates were collected every hour afterwards for 5 hrs followed by western blot analysis using Smek1 antibodies. D) The phosphorylation of Smek1 induced by stress was abolished by treating anti-Smek1 IPs with potato acid phosphatase (PAP).

FIG. 4: A) Lack of phosphorylation of GST-Smek1 by JNK MAPK in vitro. GST-cJUN was used a positive control for JNK activity. B) phosphorylation of GST-Smek1 by p38 MAPKs in vitro. Flag-tagged p38 MAPK isoforms were transfected into 293T cells, activated by stimulating cells with UV (120 J/m2), and immunoprecipitated using anti-Flag antibodies for in vitro kinase assay. GST-ATF2 was used as a positive control for p38 MAPK activity. The top panel showed the protein levels of different p38 MAPK isoforms in the lysates. The lower panel showed the differential phosphorylation of GST-Smek1 by p38 MAPKs. C) Identification of potential phosphorylation sites of Smek1. Top panel showed the autoradiograph of p38 Kinase assay using GST-Smek1 and GSTSmek1-5A mutant as substrate, respectively. GST-ATF2 was the positive control, and kinase inactive p38 delta-KM and p38 gamma-AF were negative controls; middle panel showed the protein levels of p38 delta and p38 gamma in cell lysates; the bottom panel showed the predicted p38 MAP kinase phosphorylation sites in Smek1. D) Lack of phosphorylation of Smek1-5A mutant in response to stress in vivo. 293T cells transiently expressing FLAG-tagged Smek1-5A mutant were treated with various stress stimuli as indicated, and cell lysates were analyzed by western blotting in comparison to the wild type controls shown on the left.

FIG. 5: Interaction between Smek1 and FOXO proteins. A) Left panel: 293T cells were transfected with FLAG-Smek1 in the absence or presence of HA-FOXO3a were lysed for immunoprecipitation using anti-FLAG antibodies. The immunoprecipitates were resolved by SDS-PAGE and probed with anti-HA and anti-FLAG antibodies separately to show protein levels in the IPs (top) and lysates (bottom). Right panel: similar experiment was performed with Smek1, FOXO4 and FOXO4-TM mutant. The sample lanes were numbered at the bottom for convenience. B) Left panel: 293T cells were transfected with HAFOXO3a in the absence or presence of FLAG-Smek1 or Smek1-5A mutant, followed by cell lysis, anti-FLAG immunoprecipitation and western blot analysis using anti-HA antibodies. IgG and alpha-tubulin were used as controls for protein levels in IPs (top) and lysates (bottom), respectively. Right panel: the same blot was stripped and probed with anti-FLAG antibodies to show Smek1 proteins levels in IPs (top) and lysates (bottom).

FIG. 6: Activation of FOXO3a-driven transcription by Smek1. A) Activation of a synthetic FOXO luciferase reporter by Smek1. HepG2 hepatocytes were transfected with the indicated plasmids with a synthetic luciferase reporter containing three copies of FOXO binding sites (pGL2-3xIRS) and a beta-galactosidase reporter construct. Forty hours later cell lysates were collected for luciferase assay and the data were normalized to the value of beta-galactosidase activity and presented as a percent of activity of vector control. B) Dosage-dependent activation of FOXO reporter by Smek1. 293 cells were transfected with constitutively active FOXO3a-TM mutant and various amount of Smek1 in the presence of pGL2-3xIRS and a beta-galactosidase reporter constructs. The data were normalized to the value of beta-galactosidase activity and

presented as fold of the activity by expressing FOXO3a-TM alone. C) and D) Activation of native promoters of FOXO target gene by Smek1. Cells were transfected as indicated together with a luciferase reporter driven by the native promoter of FOXO3a target genes, GADD45 and catalase, respectively. The data are shown as a percent of vector control calculated from duplicated samples.

FIG. 7: Working model. The figure shows two signaling pathways: (i) the insulin/IGF-1-PI3K-AKT signaling pathway and (ii) the stress activated pathway represented by the upstream kinase ASK1-downstream p38 MAPK cascade. The two pathways were shown to converge on a protein complex containing Smek1 and FOXO proteins in the nucleus. While AKT phosphorylation negatively regulates Smek1-FOXO interaction by excluding FOXO from the nucleus, stress signaling promotes the Smek1-FOXO interaction via phosphorylation of both Smek1 and FOXO, which represents a balance that exists under physiological circumstances. As a result, the integrated response may be translated into changes in gene expression that are important in stress resistance and life span regulation.

FIG. 8: Additional Sequences. A) shows the predicted Dictyostelium (Dictyostelium discoideum) Smek1 protein sequence (SEQ ID NO 26), B) shows the Human Smek1 cDNA sequence (SEQ ID NO 27), C) shows the Human Smek2 cDNA sequence (SEQ ID NO 28), D) shows the predicted Dictyostelium discoideum Smek1 cDNA sequence (SEQ ID NO 29), E) shows the C. elegans Smek1 cDNA sequence (SEQ ID NO 30), F) shows the S. cerevisiae Smek1 cDNA sequence (SEQ ID 31).

FIG. 9. smk-1 is required for the increased longevity of insulin/ IGF-1 signaling. In all cases, the solid black line depicts animals grown on bacteria with an empty vector all of their life. The solid grey line depicts animals grown on bacteria producing smk-1 dsRNA. In cases where daf-16 RNAi was required, the cross-hatched line depicts animals grown on bacteria expressing daf-16 RNAi. A) daf-2(e1370) long-lived mutant animals. B) N2, wild-type animals. C) isp-1(qm150) long-lived mutant animals. D) Long-lived cyc-1 RNAi (complex III) treated animals. E) daf-16(mu86) null mutant animals. F) glp -1(e2141) long-lived mutant animals. All statistical data for life span analysis can be found in Table 1.

AN	11070309 IFIPAT;IFIUDB;IFICDB
TITLE:	INCREASING LIFE SPAN BY MODULATION OF SMEK
INVENTOR(S):	Dillin; Andrew, Del Mar, CA, US Hunter; Tony, Del Mar, CA, US Ma; Hui, San Diego, CA, US Wolff; Suzanne C., Carlsbad, CA, US
PATENT ASSIGNEE(S):	The Salk Institute for Biological Studies, La Jolla, CA, US
AGENT:	MORRISON & FOERSTER LLP, 425 MARKET STREET, SAN FRANCISCO, CA, 94105-2482, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2006019314	A1	20060126
APPLICATION INFORMATION:	US 2005-165819		20050624

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2004-583284P	20040625 (Provisional)
FAMILY INFORMATION:	US 2006019314	20060126

DOCUMENT TYPE:	Utility Patent Application - First Publication
FILE SEGMENT:	CHEMICAL APPLICATION

GOVERNMENT INTEREST:

This invention was made with United States government support under Grant No. RO1 CA082683, Grant No. 5 F32 DK060367, Grant No. CA054418, and Grant No.

DK070696 from the National Institutes of Health. The United States Government has certain rights in this invention.

PARENT CASE DATA:

This application claims the benefit of U.S. Provisional Application No. 60/583,284, filed Jun. 25, 2004.

NUMBER OF CLAIMS: 21 9 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1: A) Sequence alignment of Smek orthologs from human, Drosophila, C. elegans and S. cerevisiae. B) Localization of Smek1 and Smek2 in the human genome. C) Domain structure of human Smek1

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synthetic FOXO luciferase reporter by Smek1. HepG2 hepatocytes were transfected with the indicated plasmids with a synthetic luciferase reporter containing three copies of FOXO binding sites (pGL2-3xIRS) and a beta-galactosidase reporter construct. Forty hours later cell lysates were collected for luciferase assay and the data were normalized to the value of beta-galactosidase activity and presented as a percent of activity of ***vector*** control. B) Dosage-dependent activation of FOXO reporter by Smek1. 293 cells were transfected with constitutively active FOXO3a-TM mutant and various amount of Smek1 in the presence of pGL2-3xIRS and a beta-galactosidase reporter constructs. The data were normalized to the value of beta-galactosidase activity and presented as fold of the activity by ***expressing*** FOXO3a-TM alone. C) and D) Activation of native promoters of FOXO target gene by Smek1. Cells were transfected as indicated together with a luciferase reporter driven by the native promoter of FOXO3a target genes, GADD45 and catalase, respectively. The data are shown as a percent of ***vector*** control calculated from duplicated samples.
FIG. 7: Working model. The figure shows two signaling pathways: (i) the insulin/IGF-1-PI3K-AKT signaling pathway and (ii) the stress activated pathway represented by the upstream kinase ASK1-downstream p38 MAPK cascade. The two pathways were shown to converge on a protein complex containing Smek1 and FOXO proteins in the nucleus. While AKT phosphorylation negatively regulates Smek1-FOXO interaction by excluding FOXO from the nucleus, stress signaling promotes the Smek1-FOXO interaction via phosphorylation of both Smek1 and FOXO, which represents a balance that exists under physiological circumstances. As a result, the integrated response may be translated into changes in gene ***expression*** that are important in stress resistance and life span regulation.
FIG. 8: Additional Sequences. A) shows the predicted Dictyostelium (Dictyostelium discoideum) Smek1 protein sequence (SEQ ID NO 26), B) shows the Human Smek1 cDNA sequence (SEQ ID NO 27), C) shows the Human Smek2 cDNA sequence (SEQ ID NO 28), D) shows the predicted Dictyostelium discoideum Smek1 cDNA sequence (SEQ ID NO 29), E) shows the C. elegans Smek1 cDNA sequence (SEQ ID NO 30), F) shows the S. cerevisiae Smek1 cDNA sequence (SEQ ID 31).
FIG. 9. smk-1 is required for the increased longevity of insulin/ IGF-1 signaling. In all cases, the solid black line depicts animals grown on bacteria with an empty vector all of their life. The solid grey line depicts animals grown on bacteria producing smk-1 dsRNA. In cases where daf-16 RNAi was required, the cross-hatched line depicts animals grown on bacteria expressing daf-16 RNAi. A) daf-2(e1370) long-lived mutant animals. B) N2, wild-type animals. C) isp-1(qm150) long-lived mutant animals. D) Long-lived cyc-1 RNAi (complex III) treated animals. E) daf-16(mu86) null mutant animals. F) glp-1(e2141) long-lived mutant animals.
All statistical data for life span analysis can be found in Table 1.

L12 ANSWER 3 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI Use of ICA512, or a C-terminal fragment or derivative of ICA512 for stimulating expression or promoting cell proliferation of peptide hormones in peptide-hormone secreting endocrine cells or neurons.
IN MZIAUT, H; SOLIMENA, M; TRAJKOVSKI, M
AN 2006-197398 [21] WPIDS
AB EP 1632245 A UPAB: 20060328
NOVELTY - Use of ICA512 or its derivative or fragment, or a C-terminal fragment or derivative of ICA512 for stimulating expression of peptide hormones in peptide-hormone secreting endocrine cells or neurons or for promoting cell proliferation of peptide-hormone secreting endocrine cells or neurons.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for:
(1) a method of stimulating expression of peptide hormones in peptide-hormone secreting endocrine cells or neurons;
(2) a method of promoting cell proliferation of peptide-hormone secreting endocrine cells or neurons;
(3) a method of treating or preventing type-1 or type-2 diabetes;
(4) a method of screening for an agent capable of stimulating expression of peptide hormones in peptide hormone-secreting endocrine

cells or neurons;
(5) a method of screening for an agent capable of promoting cell proliferation of peptide hormone-secreting endocrine cells or neurons;
(6) a method of screening for an agent capable of stimulating expression of insulin in pancreatic beta -cells; and
(7) a method of screening for an agent capable of promoting cell proliferation of pancreatic beta -cells.
ACTIVITY - Antidiabetic. No biological data given.
MECHANISM OF ACTION - None given.
USE - Use of ICA512 or its derivative or fragment, or a C-terminal fragment of ICA512 or a derivative above for the preparation of a pharmaceutical composition for treating or preventing type-1 or type-2 diabetes (claimed). The ICA512 or its derivative or fragment, or a C-terminal fragment or derivative of ICA512 is useful for stimulating expression of peptide hormones in peptide-hormone secreting endocrine cells or neurons or for promoting cell proliferation of peptide-hormone secreting endocrine cells or neurons.
Dwg.0/21

ACCESSION NUMBER: 2006-197398 [21] WPIDS
DOC. NO. CPI: C2006-065638
TITLE: Use of ICA512, or a C-terminal fragment or derivative of ICA512 for stimulating expression or promoting cell proliferation of peptide hormones in peptide-hormone secreting endocrine cells or neurons.
DERWENT CLASS: B04 D16
INVENTOR(S): MZIAUT, H; SOLIMENA, M; TRAJKOVSKI, M
PATENT ASSIGNEE(S): (UYDR) UNIV TECH DRESDEN MEDIZINISCHE FAKULTAE; (UYDR) UNIV DRESDEN TECH
COUNTRY COUNT: 112
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 1632245	A1	20060308	(200621)*	EN	63
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IT LI LT LU LV MC MK NL PL PT RO SE SI SK TR					
WO 2006029728	A1	20060323	(200622)	EN	
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU LV MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KM KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NG NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
EP 1632245	A1	EP 2004-20912	20040902
WO 2006029728	A1	WO 2005-EP9473	20050902

PRIORITY APPLN. INFO: EP 2004-20912 20040902

L12 ANSWER 4 OF 59 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
TI Exendin-4 induction of cyclin D1 expression in INS-1 β-cells: Involvement of cAMP-responsive element.
SO Journal of Endocrinology, (2006) Vol. 188, No. 3, pp. 623-633. .
Refs: 37
ISSN: 0022-0795 CODEN: JOENAK
AU Kim M.-J.; Kang J.-H.; Park Y.G.; Ryu G.R.; Ko S.H.; Jeong I.-K.; Koh

K.-H.; Rhie D.-J.; Yoon S.H.; Hahn S.J.; Kim M.-S.; Jo Y.-H.

AB Glucagon-like peptide-1 (GLP-1) and its analog exendin-4 (EX) have been considered as a growth factor implicated in pancreatic islet mass increase and β-cell proliferation. This study aimed to investigate the effect of EX on cyclin D1 expression, a key regulator of the cell cycle, in the pancreatic β-cell line INS-1. We demonstrated that EX significantly increased cyclin D1 mRNA and subsequently its protein levels. Although EX induced phosphorylation of Raf-1 and extracellular-signal-regulated kinase (ERK), both PD98059 and exogenous ERK1 had no effect on the cyclin D1 induction by EX. Instead, the cAMP-elevating agent forskolin induced cyclin D1 expression remarkably and this response was inhibited by pretreatment with H-89, a protein kinase A (PKA) inhibitor. Promoter analyses revealed that the cAMP-responsive element (CRE) site (at position -48; 5'-TAACGTCA-3') of cyclin D1 gene was required for both basal and EX-induced activation of the cyclin D1 promoter, which was confirmed by site-directed mutagenesis study. For EX to activate the cyclin D1 promoter effectively, CRE-binding protein (CREB) should be phosphorylated and bound to the putative CRE site, according to the results of electrophoretic mobility shift and chromatin immunoprecipitation assays. Lastly, a transfection assay employing constitutively active or dominant-negative CREB expression plasmids clearly demonstrated that CREB was largely involved in both basal and EX-induced cyclin D1 promoter activities. Taken together, EX-induced cyclin D1 expression is largely dependent on the cAMP/PKA signaling pathway, and EX increases the level of phosphorylated CREB and more potently trans-activates cyclin D1 gene through binding of the CREB to the putative CRE site, implicating a potential mechanism underlying β-cell proliferation by EX. .

ACCESSION NUMBER: 2006143685 EMBASE
TITLE: Exendin-4 induction of cyclin D1 expression in INS-1 β-cells: Involvement of cAMP-responsive element.
AUTHOR: Kim M.-J.; Kang J.-H.; Park Y.G.; Ryu G.R.; Ko S.H.; Jeong I.-K.; Koh K.-H.; Rhie D.-J.; Yoon S.H.; Hahn S.J.; Kim M.-S.; Jo Y.-H.
CORPORATE SOURCE: Y.-H. Jo, Department of Physiology, College of Medicine, The Catholic University of Korea, Seoul 137-701, Korea, Republic of. yhjo@catholic.ac.kr
SOURCE: Journal of Endocrinology, (2006) Vol. 188, No. 3, pp. 623-633. .
Refs: 37
ISSN: 0022-0795 CODEN: JOENAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Apr 2006
Last Updated on STN: 10 Apr 2006

L12 ANSWER 5 OF 59 EMBASE

TI A novel role of circadian transcription factor DBP in hippocampal plasticity.

SO Molecular and Cellular Neuroscience, (2006) Vol. 31, No. 2, pp. 303-314. .
Refs: 49
ISSN: 1044-7431 CODEN: MOCNED

AU Klugmann M.; Leichtlein C.B.; Symes C.W.; Klaussner B.C.; Brooks A.I.; Young D.; During M.J.

AB In neurons, a variety of extracellular stimuli are capable of inducing transcriptional events that underlie complex processes ranging from

learning to disease. The mechanisms linking these long-lasting cellular modifications to behavior remain to be established. Here, we show by microarray analysis that hippocampal activation of glucagon-like peptide-1 receptor (GLP-1R), which is associated with improved learning and neuroprotection, results in suppression of the transcription factor DBP (albumin D-site-binding protein). Recombinant adeno-associated virus (rAAV) based gene expression of DBP in the hippocampus of adult rats caused upregulation of mRNAs encoding constituents of the molecular clock, and the DBP target gene, pyridoxal kinase. Behaviorally, DBP over expression inhibited spatial learning but not memory, and enhanced susceptibility to kainate-induced seizures. This phenotype was paralleled by the activation of MAP kinase in dendritic regions of hippocampal neurons in vivo. These data suggest that DBP may represent an important transcriptional link between GLP-1R activation and neuroplasticity in the hippocampus.

ACCESSION NUMBER: 2006074595 EMBASE
TITLE: A novel role of circadian transcription factor DBP in hippocampal plasticity.
AUTHOR: Klugmann M.; Leichtlein C.B.; Symes C.W.; Klaussner B.C.; Brooks A.I.; Young D.; During M.J.
CORPORATE SOURCE: M. Klugmann, Department of Neurobiology, IZN, University of Heidelberg, Im Neuenheimer Feld 364, 69120 Heidelberg, Germany. m.klugmann@uni-hd.de
SOURCE: Molecular and Cellular Neuroscience, (2006) Vol. 31, No. 2, pp. 303-314. .
Refs: 49
ISSN: 1044-7431 CODEN: MOCNED
PUBLISHER IDENT.: S 1044-7431(05)00243-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
021 Developmental Biology and Teratology
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 10 Mar 2006
Last Updated on STN: 10 Mar 2006

L12 ANSWER 6 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI METHODS AND DNA CONSTRUCTS FOR HIGH YIELD PRODUCTION OF POLYPEPTIDES
INF Holmquist; Barton, Eagle, NE, US
Luan; Peng, Fishers, IN, US
Wagner; Fred W., Walton, NE, US
Xia; Yuannan, Lincoln, NE, US
IN Holmquist Barton; Luan Peng; Wagner Fred W; Xia Yuannan
AB The invention provides an inclusion body fusion partner to increase peptide and polypeptide production in a cell.
CLMN 83 13 Figure(s).
FIG. 1 is the pBN121 plasmid map. Ori=the origin of replication from pMB1; KanR=kanamycin resistance gene; Tac=tac promoter; LacIq=lac repressor gene; GST=terminator.
FIG. 2 shows a hydrophobicity plot of an inclusion body fusion partner (SEQ ID NO:1).
FIG. 3 shows the amino acid and nucleic acid sequences (SEQ ID NOs 78 and 79, respectively) for the expression cassette of pBN121-T7tagPh-CH-GRF(1-44)CH.
FIG. 4 shows the amino acid and nucleic acid sequences (SEQ ID NOs 80 and 81, respectively)for the expression cassette of pBN121-T7tagPh-CPGM-GLP-1(7-36)CHPG.
FIG. 5 shows the amino acid and nucleic acid sequences (SEQ ID NOs 82 and 83, respectively)for the expression cassette of pBN121-T7tagPh-GGGR-GLP-1(7-36)AFA.

FIG. 6 is the pBN122-M-GLP-1(7-36)AFAFGGGPG-T7tagPh plasmid map. Ori=the origin of replication from pMB1; KanR=kanamycin resistance gene; Tac=tac promoter; LacIq=lac repressor gene; GST=terminator.

FIG. 7 shows the amino acid and nucleic acid sequences (SEQ ID NOs 84 and 85, respectively)for the expression cassette of pBN122-M-GLP-1(7-36)AFAFGGGPG-T7tagPh.

FIG. 8 shows the amino acid and nucleic acid sequences (SEQ ID NOs 86 and 87, respectively)for the expression cassette of pBN121-T7tagPh-VDDR-GLP-2(1-33)A2G.

FIG. 9 is the SDS-PAGE analysis of lysates obtained from cells that contain a nucleic acid construct of the invention. Cells were lysed by sonication in 300 mu l 10 mM Tris, 1 mM EDTA (pH 8) buffer and centrifuged for 5 minutes to separate the supernatants and inclusion bodies. The inclusion bodies were resuspended in 300 mu l water and mixed with 2x sample buffer. After heating at 85 degrees C. for 10 minutes, 20 mu l of each sample was applied to the gel. Lane 1: Invitrogen Multi Mark. Lanes 2 and 3: inclusion bodies from induced HMS174 cells containing pBN121-T7tagPh-CPGM-GLP-1(7-36)CHPG. Lanes 4 and 5: inclusion bodies form induced BL21 cells containing pBN121T7tagPh-CPGM-GLP-1(7-36)CHPG. Lanes 6 and 7: inclusion bodies from induced HMS174 cells with pBN121-T7tagPh-CH-GRF(1-44)CH. Lanes 8 and 9: inclusion bodies from induced BL21 cells containing pBN121-T7tagPh-CH-GRF(1-44)CH.

FIG. 10 shows the amino acid, and nucleic acid sequences (SEQ ID NOs 88 and 89, respectively) for the expression cassette of pBN121-M-PTH(1-84).

FIG. 11 shows the amino acid and nucleic acid sequences (SEQ ID NOs 90 and 91, respectively) for the expression cassette pBN121T7tag-CH-PTH (1-84).

FIG. 12 shows the amino acid and nucleic acid sequences (SEQ ID NOs 92 and 93, respectively) for the expression cassette of pBN121-T7tagPh-CH-PTH (1-84).

FIG. 13 illustrates an SDS-PAGE analysis. Lane 1: lysate from induced BL21 cells containing pBN121-M-PTH(1-84). Lane 2: lysate from induced BL21 cells containing pBN121-T7tag-CH-PTH(184). Lane 3: lysate from induced BL21 cells containing pBN121T7tagPh-CH-PTH(1-84).

AN	11000432 IFIPAT;IFIUDB;IFICDB		
TITLE:	METHODS AND DNA CONSTRUCTS FOR HIGH YIELD PRODUCTION OF POLYPEPTIDES		
INVENTOR(S):	Holmquist; Barton, Eagle, NE, US Luan; Peng, Fishers, IN, US Wagner; Fred W., Walton, NE, US Xia; Yuannan, Lincoln, NE, US		
PATENT ASSIGNEE(S):	Unassigned		
AGENT:	Schwegman, Lundberg, Woessner & Kluth, P.A., P.O. Box 2938, Minneapolis, MN, 55402, US		

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2005239172	A1	20051027
APPLICATION INFORMATION:	US 2004-997700		20041124

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	WO 2003-US16645	20030523	PENDING

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	US 2002-383212P	20020524	(Provisional)
FAMILY INFORMATION:	US 2005239172	20051027	

DOCUMENT TYPE:	Utility Patent Application - First Publication
FILE SEGMENT:	CHEMICAL APPLICATION
NUMBER OF CLAIMS:	83 13 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 is the pBN121 plasmid map. Ori=the origin of replication from pMB1; KanR=kanamycin resistance gene; Tac=tac promoter; LacIq=lac repressor gene; GST=terminator.

FIG. 2 shows a hydrophobicity plot of an inclusion body fusion partner (SEQ ID NO:1).

FIG. 3 shows the amino acid and nucleic acid sequences (SEQ ID NOs 78 and 79, respectively) for the expression cassette of pBN121-T7tagPh-CH-GRF(1-44)CH.

FIG. 4 shows the amino acid and nucleic acid sequences (SEQ ID NOs 80 and 81, respectively)for the expression cassette of pBN121-T7tagPh-CPGM-GLP-1(7-36)CHPG.

FIG. 5 shows the amino acid and nucleic acid sequences (SEQ ID NOs 82 and 83, respectively)for the expression cassette of pBN121-T7tagPh-GGGR-GLP-1(7-36)AFA.

FIG. 6 is the pBN122-M-GLP-1(7-36)AFAFGGGPG-T7tagPh plasmid map. Ori=the origin of replication from pMB1; KanR=kanamycin resistance gene; Tac=tac promoter; LacIq=lac repressor gene; GST=terminator.

FIG. 7 shows the amino acid and nucleic acid sequences (SEQ ID NOs 84 and 85, respectively)for the expression cassette of pBN122-M-GLP-1(7-36)AFAFGGGPG-T7tagPh.

FIG. 8 shows the amino acid and nucleic acid sequences (SEQ ID NOs 86 and 87, respectively)for the expression cassette of pBN121-T7tagPh-VDDR-GLP-2(1-33)A2G.

FIG. 9 is the SDS-PAGE analysis of lysates obtained from cells that contain a nucleic acid construct of the invention. Cells were lysed by sonication in 300 mu l 10 mM Tris, 1 mM EDTA (pH 8) buffer and centrifuged for 5 minutes to separate the supernatants and inclusion bodies. The inclusion bodies were resuspended in 300 mu l water and mixed with 2x sample buffer. After heating at 85 degrees C. for 10 minutes, 20 mu l of each sample was applied to the gel. Lane 1: Invitrogen Multi Mark. Lanes 2 and 3: inclusion bodies from induced HMS174 cells containing pBN121-T7tagPh-CPGM-GLP-1(7-36)CHPG. Lanes 4 and 5: inclusion bodies form induced BL21 cells containing pBN121T7tagPh-CPGM-GLP-1(7-36)CHPG. Lanes 6 and 7: inclusion bodies from induced HMS174 cells with pBN121-T7tagPh-CH-GRF(1-44)CH. Lanes 8 and 9: inclusion bodies from induced BL21 cells containing pBN121-T7tagPh-CH-GRF(1-44)CH.

FIG. 10 shows the amino acid, and nucleic acid sequences (SEQ ID NOs 88 and 89, respectively) for the expression cassette of pBN121-M-PTH(1-84).

FIG. 11 shows the amino acid and nucleic acid sequences (SEQ ID NOs 90 and 91, respectively) for the expression cassette pBN121T7tag-CH-PTH (1-84).

FIG. 12 shows the amino acid and nucleic acid sequences (SEQ ID NOs 92 and 93, respectively) for the expression cassette of pBN121-T7tagPh-CH-PTH (1-84).

FIG. 13 illustrates an SDS-PAGE analysis. Lane 1: lysate from induced BL21 cells containing pBN121-M-PTH(1-84). Lane 2: lysate from induced BL21 cells containing pBN121-T7tag-CH-PTH(184). Lane 3: lysate from induced BL21 cells containing pBN121T7tagPh-CH-PTH(1-84).

L12 ANSWER 7 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN

TI METHODS AND DNA CONSTRUCTS FOR HIGH YIELD PRODUCTION OF POLYPEPTIDES

INF Harley; Scott, Pensacola, FL, US
Luan; Peng, Fishers, IN, US
Williams; James A., Lincoln, NE, US
Xia; Yuannan, Lincoln, NE, US

IN Harley Scott; Luan Peng; Williams James A; Xia Yuannan

AB The invention provides an inclusion body fusion partner to increase peptide and polypeptide production in a cell.

CLMN 82 19 Figure(s).

FIG. 1 is a plasmid map for the pBN95 Expression Plasmid .

FIG. 2 is a plasmid map for the pBN95(Tac)-T7tagVgCH-GRF(1-44)A plasmid.

FIG. 3 illustrates the nucleic acid and amino acid sequence for the T7tagVgCH-GRF(1-44)A cassette. The leader sequence, Vg sequence, Linker sequence, and GRF(1-44)A sequences are indicated by bracketed lines. Restriction enzyme recognition sites are indicated by name and by underlining. The cleavage site is indicated by an arrow.

FIG. 4 illustrates the nucleic acid and amino acid sequence for the

T7tag-GRF(1-44)A cassette. The T7tag, linker, and GRF(1-44) A nucleic acid and amino acid sequences are indicated. Restriction enzyme recognition sites are indicated by name and by underlining. An enterokinase recognition site is indicated by an arrow.

FIG. 5 illustrates the nucleic acid and amino acid sequence for the T7tagVg-GRF(1-44)A cassette. The leader sequence, Vg sequence, Linler sequence, and GRF(1-44)A sequences are indicated by bracketed lines. Restriction enzyme recognition sites are indicated by name and by underlining. The cleavage site is indicated by an arrow. The stop codon is labeled and indicated by stars.

FIG. 6 illustrates the nucleic acid and amino acid sequence for the T7tagVg(opt)CH-GRF(1-44)A cassette. Optimized codons are underlined. The stop codon is indicated with a star.

FIG. 7 illustrates a hydrophobicity plot for an inclusion body fusion partner having SEQ ID NO: 2.

FIG. 8 illustrates the nucleic acid and amino acid sequence for the T7tagVgMut1CH-GRP(1-44)A cassette. Amino acid substitutions are indicated as being encoded by codons in lower case. Restriction enzyme recognition sites are indicated by name. The stop codon is indicated with a star.

FIG. 9 illustrates the nucleic acid and amino acid sequence for the T7tagVgMut4CH-GRF(1-44)A cassette. Amino acid substitutions are indicated by lower cases letters. The stop codon is indicated with a star.

FIG. 10 illustrates the nucleic acid and amino acid sequence for the T7tagVg-PTH(1-34) cassette. A thrombin cleavage site is located between amino acids at positions 55 and 56. Restriction sites are indicated by underlining and name.

FIG. 11 illustrates the nucleic acid and amino acid sequence for a linker sequence containing a paladium cleavage site located between amino acids at position 16 and 17. The T7tag, linker, and Pd cleavage sequences are indicated.

FIG. 12 provides DNA and peptide sequences of the pET23 T7tagVg(Del3)-CHPTH(1-34) and pET23T7TagVg(Del2+3)CHPTH(1-34) expression cassettes encoding the PTH precursor peptide. Optimized codons are indicated with underlining, and restriction enzyme recognition sites are indicated by name and by underlining.

FIG. 13 is a plasmid map for the pBN115-T7tagVg-CAT plasmid.

FIG. 14 illustrates the nucleic acid and amino acid sequence for a NheI-releaseable T7Vg fragment. Restriction enzyme recognition sites are indicated by name.

FIG. 15 is a plasmid map for the pBN115-T7tagVg-LacZ plasmid.

FIG. 16 illustrates an SDS-PAGE gel of samples obtained from cells that were treated according to the indicated conditions. Lane 1: Novex multimark molecular weight marker; Lane 2: 37 degrees C., induced 2 hr, soluble fraction of pBN115(Tac)T7tagVg-LacZ; Lane 3: 37 degrees C., uninduced, soluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 4: 27 degrees C., induced 2 hr, soluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 5: 27 degrees C., uninduced, soluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 6: 37 degrees C., induced 2 hr, insoluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 7: 37 degrees C., uninduced, insoluble fraction of pBN115(Tac)T7tagVg-LacZ; Lane 8: 27 degrees C., induced 2 hr, insoluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 9: 27 degrees C., uninduced, insoluble fraction of pBN115(Tac)-T7tagVg-LacZ.

FIG. 17 illustrates the nucleic acid and amino acid sequence of a T7tagVgCH-GLP-1(7-36)CH cassette. A restriction enzyme recognition site is indicated by name.

FIG. 18 illustrates a generalized structure of a polypeptide of the invention.

FIG. 19 illustrates a series of amino acid deletions occurring around the hydrophobic core of SEQ ID NO:2.

AN 10982705 IFIPAT;IFIUDB;IFICDB

TITLE: METHODS AND DNA CONSTRUCTS FOR HIGH YIELD PRODUCTION OF POLYPEPTIDES

INVENTOR(S): Harley; Scott, Pensacola, FL, US
Luan; Peng, Fishers, IN, US
Williams; James A., Lincoln, NE, US
Xia; Yuannan, Lincoln, NE, US
PATENT ASSIGNEE(S): Unassigned
AGENT: Schwegman, Lundberg, Woessner & Kluth, P.A., P.O. Box 2938, Minneapolis, MN, 55402, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2005221444	A1	20051006
APPLICATION INFORMATION:	US 2004-997078		20041124

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	WO 2003-US16643	20030523	PENDING

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	US 2002-383370P	20020524	(Provisional)
FAMILY INFORMATION:	US 2005221444	20051006	

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 82 19 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 is a plasmid map for the pBN95 Expression Plasmid.

FIG. 2 is a plasmid map for the pBN95(Tac)-T7tagVgCH-GRF(1-44)A ***plasmid.***

FIG. 3 illustrates the nucleic acid and amino acid sequence for the T7tagVgCH-GRF(1-44)A cassette. The leader sequence, Vg sequence, Linker sequence, and GRF(1-44)A sequences are indicated by bracketed lines. Restriction enzyme recognition sites are indicated by name and by underlining. The cleavage site is indicated by an arrow.

FIG. 4 illustrates the nucleic acid and amino acid sequence for the T7tag-GRF(1-44)A cassette. The T7tag, linker, and GRF(1-44) A nucleic acid and amino acid sequences are indicated. Restriction enzyme recognition sites are indicated by name and by underlining. An enterokinase recognition site is indicated by an arrow.

FIG. 5 illustrates the nucleic acid and amino acid sequence for the T7tagVg-GRF(1-44)A cassette. The leader sequence, Vg sequence, Linler sequence, and GRF(1-44)A sequences are indicated by bracketed lines. Restriction enzyme recognition sites are indicated by name and by underlining. The cleavage site is indicated by an arrow. The stop codon is labeled and indicated by stars.

FIG. 6 illustrates the nucleic acid and amino acid sequence for the T7tagVg(opt)CH-GRF(1-44)A cassette. Optimized codons are underlined. The stop codon is indicated with a star.

FIG. 7 illustrates a hydrophobicity plot for an inclusion body fusion partner having SEQ ID NO: 2.

FIG. 8 illustrates the nucleic acid and amino acid sequence for the T7tagVgMut1CH-GRP(1-44)A cassette. Amino acid substitutions are indicated as being encoded by codons in lower case. Restriction enzyme recognition sites are indicated by name. The stop codon is indicated with a star.

FIG. 9 illustrates the nucleic acid and amino acid sequence for the T7tagVgMut4CH-GRF(1-44)A cassette. Amino acid substitutions are indicated by lower cases letters. The stop codon is indicated with a star.

FIG. 10 illustrates the nucleic acid and amino acid sequence for the T7tagVg-PTH(1-34) cassette. A thrombin cleavage site is located between amino acids at positions 55 and 56. Restriction sites are indicated by underlining and name.

FIG. 11 illustrates the nucleic acid and amino acid sequence for a linker

sequence containing a paladium cleavage site located between amino acids at position 16 and 17. The T7tag, linker, and Pd cleavage sequences are indicated.
FIG. 12 provides DNA and peptide sequences of the pET23 T7tagVg(Del3)-CHPTH(1-34) and pET23T7TagVg(Del2+3)CHPTH(1-34) expression cassettes encoding the PTH precursor peptide. Optimized codons are indicated with underlining, and restriction enzyme recognition sites are indicated by name and by underlining.
FIG. 13 is a plasmid map for the pBN115-T7tagVg-CAT plasmid
.
FIG. 14 illustrates the nucleic acid and amino acid sequence for a NheI-releaseable T7Vg fragment. Restriction enzyme recognition sites are indicated by name.
FIG. 15 is a plasmid map for the pBN115-T7tagVg-LacZ plasmid
.
FIG. 16 illustrates an SDS-PAGE gel of samples obtained from cells that were treated according to the indicated conditions. Lane 1: Novex multimark molecular weight marker; Lane 2: 37 degrees C., induced 2 hr, soluble fraction of pBN115(Tac)T7tagVg-LacZ; Lane 3: 37 degrees C., uninduced, soluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 4: 27 degrees C., induced 2 hr, soluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 5: 27 degrees C., uninduced, soluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 6: 37 degrees C., induced 2 hr, insoluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 7: 37 degrees C., uninduced, insoluble fraction of pBN115(Tac)T7tagVg-LacZ; Lane 8: 27 degrees C., induced 2 hr, insoluble fraction of pBN115(Tac)-T7tagVg-LacZ; Lane 9: 27 degrees C., uninduced, insoluble fraction of pBN115(Tac)-T7tagVg-LacZ.
FIG. 17 illustrates the nucleic acid and amino acid sequence of a T7tagVgCH-GLP-1(7-36)CH cassette. A restriction enzyme recognition site is indicated by name.
FIG. 18 illustrates a generalized structure of a polypeptide of the invention.
FIG. 19 illustrates a series of amino acid deletions occurring around the hydrophobic core of SEQ ID NO:2.

L12 ANSWER 8 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI BACTERIAL HOST CELL FOR THE DIRECT EXPRESSION OF PEPTIDES
INF Consalvo; Angelo P., Monroe, NY, US
Meenan; Christopher P., Lincoln Park, NJ, US
Mehta; Nozer M., Randolph, NJ, US
Ray; Martha V.L., Nutley, NJ, US
IN Consalvo Angelo P; Meenan Christopher P; Mehta Nozer M; Ray Martha V L
AB Expression systems are disclosed for the direct expression of peptide products into the culture media where genetically engineered host cells are grown. High yield was achieved with a special selection of hosts, and/or fermentation processes which include careful control of cell growth rate, and use of an inducer during growth phase. Special universal cloning vectors are provided for the preparation of expression vectors which include control regions having multiple promoters linked operably with coding regions encoding a signal peptide upstream from a coding region encoding the peptide of interest. Multiple transcription cassettes are also used to increase yield. The production of amidated peptides using the expression systems is also disclosed.
CLMN 81 4 Figure(s).
FIGS. 1A, 1B and 1C show a schematic diagram of the construction of the pUSEC-03 vector (1A) which is used in the construction of the pUSEC-05 vector (1B) which is in turn used in the construction of vector pUSEC-051Q (IC) (ATCC Accession Number PTA-5567).
FIGS. 2A and 2B show a schematic diagram of the construction of the pCPM-00 vector (2A) which is used in the construction of the pUSEC-06 vector (2B)(ATCC Accession Number PTA-5568).
FIGS. 3A, 3B and 3C show a schematic diagram of the ligation of a generic peptide termed peptide X into the secretion expression vector pUSEC-051Q (3A) to generate vector pPEPX-01 which is used along with vector pUSEC-06 to construct a monogenic production vector pPEPX-02 (3B) which is used to construct a digenic production vector pPEPX-03.
FIG. 4 shows a schematic diagram of the construction of the pSCT038

vector. pSCT-038 was used to transform E. coli BLR and BLM6 and produce the digenic UGL 703 and UGL801 clones, respectively.

AN 10982703 IFIPAT;IFIUDB;IFICDB
TITLE: BACTERIAL HOST CELL FOR THE DIRECT EXPRESSION OF PEPTIDES
INVENTOR(S): Consalvo; Angelo P., Monroe, NY, US
Meenan; Christopher P., Lincoln Park, NJ, US
Mehta; Nozer M., Randolph, NJ, US
Ray; Martha V.L., Nutley, NJ, US
PATENT ASSIGNEE(S): Unigene Laboratories Inc., US
AGENT: OSTROLENK FABER GERB & SOFFEN, 1180 AVENUE OF THE AMERICAS, NEW YORK, NY, 100368403, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2005221442	A1	20051006
APPLICATION INFORMATION:	US 2005-76260		20050309

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2004-552824P	20040312 (Provisional)
FAMILY INFORMATION:	US 2005221442	20051006

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 81 4 Figure(s).
DESCRIPTION OF FIGURES:
FIGS. 1A, 1B and 1C show a schematic diagram of the construction of the pUSEC-03 vector (1A) which is used in the construction of the pUSEC-05 vector (1B) which is in turn used in the construction of ***vector*** pUSEC-051Q (IC) (ATCC Accession Number PTA-5567).
FIGS. 2A and 2B show a schematic diagram of the construction of the pCPM-00 ***vector*** (2A) which is used in the construction of the pUSEC-06 ***vector*** (2B)(ATCC Accession Number PTA-5568).
FIGS. 3A, 3B and 3C show a schematic diagram of the ligation of a generic peptide termed peptide X into the secretion expression vector pUSEC-051Q (3A) to generate vector pPEPX-01 which is used along with ***vector*** pUSEC-06 to construct a monogenic production vector pPEPX-02 (3B) which is used to construct a digenic production vector pPEPX-03.
FIG. 4 shows a schematic diagram of the construction of the pSCT038 ***vector.*** pSCT-038 was used to transform E. coli BLR and BLM6 and produce the digenic UGL 703 and UGL801 clones, respectively.

L12 ANSWER 9 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI New genetically engineered Escherichia coli bacterium that is deficient in chromosomal genes rec A and ptr encoding for recombinant protein and Protease III, respectively, useful in producing an amidated peptide product.
IN CONSALVO, A P; MEENAN, C P; MEHTA, N M; RAY, M V L
AN 2005-649544 [66] WPIDS
AB WO2005089182 A UPAB: 20051014
NOVELTY - A new genetically engineered Escherichia coli bacterium is deficient in chromosomal genes rec A and ptr encoding for recombinant protein and Protease III, respectively.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) a cloning vector;
(2) a host cell transformed or transfected with the vector;
(3) preparing an expression vector containing transcription cassettes, each cassette comprising:
(a) a coding region with nucleic acids coding for a peptide product coupled in reading frame 3' of nucleic acids coding for a signal peptide;

and

(b) a control region linked operably with the coding region, the control region comprising promoters;

(4) producing a peptide product;

(5) producing an amidated peptide product; and

(6) a recombinant cell line UGL810 having ATCC Accession Number PTA-5502 or UGL820 having ATCC Access Number PTA-5569.

USE - The genetically engineered Escherichia coli bacterium is useful in producing an amidated peptide product.

Dwg.0/4

ACCESSION NUMBER: 2005-649544 [66] WPIDS
DOC. NO. CPI: C2005-195667
TITLE: New genetically engineered Escherichia coli bacterium that is deficient in chromosomal genes rec A and ptr encoding for recombinant protein and Protease III, respectively, useful in producing an amidated peptide product.
DERWENT CLASS: B04 D16
INVENTOR(S): CONSALVO, A P; MEENAN, C P; MEHTA, N M; RAY, M V L
PATENT ASSIGNEE(S): (UNIG-N) UNIGENE LAB INC
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005089182	A2	20050929	(200566)*	EN	63
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IS IT KE LS LT LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SM SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
US 2005221442	A1	20051006	(200566)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005089182	A2	WO 2005-US7873	20050310
US 2005221442	A1 Provisional	US 2004-552824P	20040312
		US 2005-76260	20050309

PRIORITY APPLN. INFO: US 2005-76260 20050309; US 2004-552824P 20040312

L12 ANSWER 10 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI Stimulating production of secretory granules in peptide hormone-secreting endocrine cells or neurons, useful for treating/preventing diabetes, involves promoting presence of polypyrimide tract binding protein in cytoplasm of cells.
IN KNOCH, K; SOLIMENA, M
AN 2005-233181 [24] WPIDS
AB WO2005023231 A UPAB: 20050414
NOVELTY - Stimulating (M1) production of secretory granules in peptide hormone-secreting endocrine cells or neurons, involves promoting the presence of polypyrimidine tract binding protein (PTB) or its biologically active fragment or derivative in the cytoplasm of the cells.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) treating or preventing (M2) type-1 or type-2 diabetes, involves stimulating production of insulin-containing secretory granules in pancreatic beta -cells, where the stimulation comprises the step of

promoting the presence or activity of PTB or its biologically active fragment or derivative in the cytoplasm of the beta -cells;

(2) use of an agent (I) for the promotion or reduction of the presence or activity of PTB or its biologically active fragment or derivative in beta -cells for the preparation of a pharmaceutical composition for treating or preventing type-1 or type-2 diabetes, or in hypothalamic neurons for the preparation of a pharmaceutical composition for treating or preventing sleep disorders or depression, respectively;

(3) screening for an agent capable of stimulating or reducing production of secretory granules in peptide hormone-secreting endocrine cells or neurons;

(4) screening for an agent useful as a cure for sleeping disorders of depression, or as a cure for type-1 or type-2 diabetes; and

(5) use of an agent (II) reducing or blocking the presence of activity of PTB or its biologically active fragment or derivative in endocrine cells for the preparation of a pharmaceutical composition for treating or preventing hyperprolactinemia or agromegaly.

ACTIVITY - Antidiabetic; Hypnotic; Osteopathic; Endocrine-Gen. No supporting data is given.

MECHANISM OF ACTION - PTB activity promoter.

USE - (M1) is useful for stimulating production of secretory granules in peptide hormone-secreting endocrine cells or neurons. (M2) is useful for treating or preventing type-1 or type-2 diabetes. (I) is useful for promotion or reduction of presence or activity of PTB or its biologically active fragment or derivative, for the treatment of type 1 or type 2 diabetes or sleep disorders or depression. (II) is useful for reducing or blocking the presence or activity of PTB or its biologically active fragment or derivative, for the preparation of pharmaceutical composition for treatment of hyperprolactinemia or agromegaly (all claimed).

Dwg.0/13

ACCESSION NUMBER: 2005-233181 [24] WPIDS
DOC. NO. NON-CPI: N2005-192160
DOC. NO. CPI: C2005-073910
TITLE: Stimulating production of secretory granules in peptide hormone-secreting endocrine cells or neurons, useful for treating/preventing diabetes, involves promoting presence of polypyrimide tract binding protein in cytoplasm of cells.
DERWENT CLASS: B04 D16 S03
INVENTOR(S): KNOCH, K; SOLIMENA, M
PATENT ASSIGNEE(S): (PLAC) MAX PLANCK GES FOERDERUNG WISSENSCHAFTEN; (UYDR) UNIV TECH DRESDEN MEDIZINISCHE FAKULTAE
COUNTRY COUNT: 108
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2005023231	A1	20050317	(200524)*	EN	87

RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2005023231	A1	WO 2004-EP10167	20040910

PRIORITY APPLN. INFO: EP 2004-3429 20040216; EP

2003-20640 20030910

L12 ANSWER 11 OF 59 USPAT2 on STN
TI Production of heterologous polypeptides in yeast
IN Andersen, Asser Sloth, Herlev, DENMARK
Diers, Ivan, Vaerlose, DENMARK
AB A process for producing high amount of proteins or polypeptides in yeast is disclosed. The process makes use of the CIT1 yeast promoter or a functional part or variant thereof. Examples of polypeptides which are expressed in high yields are insulin or insulin analogues or GLP1.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2005:23309 USPAT2		
TITLE:	Production of heterologous polypeptides in yeast		
INVENTOR(S):	Andersen, Asser Sloth, Herlev, DENMARK Diers, Ivan, Vaerlose, DENMARK		
PATENT ASSIGNEE(S):	Novo Nordisk A/S, Bagsvaerd, DENMARK (non-U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6861237	B2	20050301
APPLICATION INFO.:	US 2001-2826		20011130 (10)
	NUMBER		DATE
PRIORITY INFORMATION:	DK 2000-1800		20001130
	US 2000-256602P		20001219 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Guzo, David		
LEGAL REPRESENTATIVE:	Green, Reza, Smith, Len, Bork, Richard		
NUMBER OF CLAIMS:	19		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	2 Drawing Figure(s); 2 Drawing Page(s)		
LINE COUNT:	679		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 12 OF 59 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
TI Glucagon-like peptide-1 protects beta cells from cytokine-induced apoptosis and necrosis: Role of protein kinase B.
SO Diabetologia, (2005) Vol. 48, No. 7, pp. 1339-1349. .
Refs: 55
ISSN: 0012-186X CODEN: DBTGAJ
AU Li L.; El-Kholy W.; Rhodes C.J.; Brubaker P.L.
AB Aims/hypothesis: The gut hormone glucagon-like peptide-1 (GLP-1) decreases beta cell apoptosis in a protein kinase B (PKB)-dependent fashion, and increases islet cell mass and function in vivo. In contrast, cytokines induce beta cell apoptosis, leading to decreased islet mass and type 1 diabetes. In the present study we used rat INS-1E beta cells and primary rat islet cells to examine the potential role of PKB as a mediator of the effect of GLP-1 on cytokine-induced apoptosis.
Methods: Cell viability was determined by MTT assay, and apoptosis and necrosis by Hoechst 33342-propidium iodide staining. Immunoblot analysis was used to detect changes in protein expression, including active (phosphorylated) and total PKB, phosphorylated and total glycogen synthase kinase-3β, activated caspase-3 and inducible nitric oxide synthase. Reactive oxygen species were determined by 1,7-dichlorofluorescein (DCF) analysis, and mutant forms of PKB were introduced into cells using adenoviral vectors. Results: Incubation of INS-1E cells with cytokines (IL-1β, TNF-α and interferon-γ; 10-50 ng/ml) for 18 h significantly decreased cell

viability (by 44%, p<0.001), cell proliferation (by 80%, p<0.001), and activation of PKB (by 67%, p<0.001). Pre-treatment with exendin -4 (10(-7) mol/l), a long-acting GLP-1 receptor agonist, partially protected the cells against cytokine-induced toxicity (p<0.01) in association with a reduction in cytokine-induced inhibition of PKB phosphorylation (p<0.05). Exendin-4 pre-treatment did not change cell proliferation. Cytokine treatment increased apoptosis (by 156%, p<0.05) and necrosis (from undetectable to 2.6% of cells). These increases were both reduced by pre-treatment with exendin-4 (p<0.05-0.01). Furthermore, cytokine-induced apoptosis and necrosis were significantly increased in cells infected with kinase-dead PKB (p<0.05), and the protective effect of exendin-4 on both parameters was fully abolished in these cells. Similar changes were observed in primary islet cells. In parallel with these changes, exendin-4 decreased the cytokine-induced activation of caspase-3 (by 46%, p<0.05), and decreased levels of inducible nitric oxide synthase (by 71%, p<0.05) and reactive oxygen species (by 27%, p<0.05). Conclusions/interpretation: The results of our study indicate that GLP-1 plays a protective role against cytokine-induced apoptosis and necrosis in beta cells through a PKB-dependent signalling pathway. .COPYRGT. Springer-Verlag 2005.

ACCESSION NUMBER: 2005381759 EMBASE
TITLE: Glucagon-like peptide-1 protects beta cells from cytokine-induced apoptosis and necrosis: Role of protein kinase B.
AUTHOR: Li L.; El-Kholy W.; Rhodes C.J.; Brubaker P.L.
CORPORATE SOURCE: P.L. Brubaker, Department of Physiology, University of Toronto, Medical Sciences Building, 1 King's College Circle, Toronto, Ont. M5S 1A8, Canada. p.brubaker@utoronto.ca
SOURCE: Diabetologia, (2005) Vol. 48, No. 7, pp. 1339-1349. .
Refs: 55
ISSN: 0012-186X CODEN: DBTGAJ
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 22 Sep 2005
Last Updated on STN: 22 Sep 2005

L12 ANSWER 13 OF 59 EMBASE DUPLICATE 1
TI Engineered β-cells secreting dipeptidyl peptidase IV-resistant glucagon-like peptide-1 show enhanced glucose-responsiveness.
SO Life Sciences, (28 Jan 2005) Vol. 76, No. 11, pp. 1239-1248. .
Refs: 22
ISSN: 0024-3205 CODEN: LIFSAK
AU Islam M.S.; Rahman S.A.; Mirzaei Z.; Islam K.B.
AB Type 2 diabetes is a polygenic disorder characterized by increased insulin resistance, and impaired insulin secretion leading to abnormalities of glucose and lipid metabolism. Reduced responsiveness of the β-cells to glucose is a critical feature of this syndrome. Glucagon-like peptide 1, a product of the pro-glucagon gene makes β-cells competent and has many other anti-diabetic properties. We speculated whether GLP-1 -based gene therapy could be an approach for treatment of type 2 diabetes. We started with a clone of rat insulinoma cells (S4 cells), which showed reduced responsiveness to glucose in terms of insulin secretion. We transfected these cells with a plasmid encoding a mutated form of GLP-1 (GLP-1-Gly8), which is

resistant to the degrading enzyme dipeptidyl-peptidase IV. Activity of secreted GLP-1-Gly8 was assayed using Chinese hamster lung fibroblasts (CHL) cells that expressed cloned GLP -1 receptor and that were transfected with CRE-Luc. Stable cell lines (Glipsulin cells) obtained by this means produced and stored immunoreactive GLP-1-Gly8. In addition to insulin, the Glipsulin cells secreted the GLP-1-Gly8. The secreted GLP-1-Gly8 was active as evidenced by the ability of the conditioned media to elevate cAMP levels in CHL cells expressing GLP-1 receptors. Glipsulin cells responded to glucose with a 6.8 fold increase in insulin secretion compared to a 2.2 fold increase in the control cells. Our results demonstrate that prolonged exposure to GLP-1-Gly8 secreted by increases glucose-responsiveness of these cells. We speculate that engineering GLP-1-Gly8 secretion by β-cells is a potential gene therapeutic strategy to treat diabetes. .

ACCESSION NUMBER: 2005028200 EMBASE
TITLE: Engineered β-cells secreting dipeptidyl peptidase IV-resistant glucagon-like peptide-1 show enhanced glucose-responsiveness.
AUTHOR: Islam M.S.; Rahman S.A.; Mirzaei Z.; Islam K.B.
CORPORATE SOURCE: shaisl@ki.se
SOURCE: Life Sciences, (28 Jan 2005) Vol. 76, No. 11, pp. 1239-1248. .
Refs: 22
ISSN: 0024-3205 CODEN: LIFSAK
PUBLISHER IDENT.: S 0024-3205(04)00950-6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jan 2005
Last Updated on STN: 27 Jan 2005

L12 ANSWER 14 OF 59 EMBASE
TI Glucagon-like peptide-1 plasmid construction and delivery for the treatment of type 2 diabetes.
SO Molecular Therapy, (2005) Vol. 12, No. 5, pp. 885-891. .
Refs: 32
ISSN: 1525-0016 CODEN: MTOHCK
AU Choi S.; Oh S.; Lee M.; Kim S.W.
AB Glucagon-like peptide-1 (GLP-1) is a 30-amino-acid hormone produced by intestinal L cells. It has been proposed that GLP-1 can be used as a new treatment for type 2 diabetes mellitus because it acts to augment insulin secretion and its effectiveness is maintained in type 2 diabetic patients. Despite its many remarkable advantages as a therapeutic agent for diabetes, GLP-1 is not immediately clinically applicable because of its extremely short half-life. One way to overcome this drawback is GLP1 gene delivery, which enables GLP-1 production in the body. In this study, the effect of GLP1 gene delivery was evaluated both in vitro and in vivo using a new plasmid constructed with a GLP1 (7-37) cDNA. The expression of the GLP1 gene was driven by a SV40 promoter/enhancer. To increase the expression level of GLP-1, nuclear factor κB binding sites were introduced. The in vitro results showed expression of GLP-1 and in vitro activity of GLP-1

, which is a glucose-dependent insulinotropic action. A single systemic administration of polyethyleneimine/pSIGLP1NF κB complex into DIO mice resulted in increasing insulin secretion and decreasing blood glucose levels for a duration longer than 2 weeks. Copyright . COPYRGT. The American Society of Gene Therapy.

ACCESSION NUMBER: 2005514067 EMBASE
TITLE: Glucagon-like peptide-1 plasmid construction and delivery for the treatment of type 2 diabetes.
AUTHOR: Choi S.; Oh S.; Lee M.; Kim S.W.
CORPORATE SOURCE: S.W. Kim, Center for Controlled Chemical Delivery, Department of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, 30 South 2000 East, Salt Lake City, UT 84112-5820, United States. rburns@pharm.utah.edu
SOURCE: Molecular Therapy, (2005) Vol. 12, No. 5, pp. 885-891. . Refs: 32
ISSN: 1525-0016 CODEN: MTOHCK
PUBLISHER IDENT.: S 1525-0016(05)00190-5
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
006 Internal Medicine
022 Human Genetics
030 Pharmacology
037 Drug Literature Index
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Dec 2005
Last Updated on STN: 1 Dec 2005

L12 ANSWER 15 OF 59 EMBASE
TI Exogenous expression of glucagon-like peptide 1 receptor and human insulin in AtT-20 corticotrophs confers cAMP-mediated gene transcription and insulin secretion.
SO Journal of Endocrinology, (2005) Vol. 187, No. 3, pp. 419-427. . Refs: 21
ISSN: 0022-0795 CODEN: JOENAK
AU Sidhu K.K.; Fowkes R.C.; Skelly R.H.; Burrin J.M.
AB The insulinotrophic effects of glucagon-like peptide 1 (GLP-1) are mediated by its seven-transmembrane receptor (GLP-1R) in pancreatic β-cells. We have transiently transfected the GLP-1R and a proopiomelanocortin (POMC) promoter-driven human preproinsulin gene vector (pIRES) into the AtT-20 pituitary corticotrophic cell line, to investigate the possibility of creating a regulated, insulin-expressing cell line. Receptor expression was confirmed by RT-PCR and functionality was demonstrated by measuring changes in cAMP levels in response to GLP-1. Rapid (5 min) stimulation of cAMP production was observed with 100 nM GLP-1, 24 h after transfection of 2 μg GLP-1R DNA. AtT-20 cells co-transfected with GLP-1R and human glycoprotein hormone α-subunit or rat POMC promoters revealed GLP-1-stimulated cAMP activation of transcription. Co-transfection of the pIRES vector with the GLP-1R resulted in GLP-1-stimulated activation of POMC promoter-driven preproinsulin gene transcription but insulin secretion was not detected. However, using an adenoviral expression system to infect AtT-20 cells with GLP-1R and the preproinsulin gene (including 120 bp of its own promoter) resulted in a 6.4 ± 0.6-fold increase in cAMP and a 4.9 ± 0.8-fold increase in insulin secretion in response to 100 nM GLP-1. These results demonstrate, for the first time, functional GLP-1R-mediated preproinsulin gene transcription and secretion in a transplantable cell line. .COPYRGT. 2005 Society for Endocrinology.

ACCESSION NUMBER: 2006007198 EMBASE
TITLE: Exogenous expression of glucagon-like peptide 1 receptor and human insulin in AtT-20 corticotrophs confers cAMP-mediated gene transcription and insulin secretion.
AUTHOR: Sidhu K.K.; Fowkes R.C.; Skelly R.H.; Burrin J.M.
CORPORATE SOURCE: K.K. Sidhu, Centre for Molecular Endocrinology, William Harvey Research Institute, Queen Mary University of London, West Smithfield, London EC1A 7BE, United Kingdom. k.k.sidhu@qmul.ac.uk
SOURCE: Journal of Endocrinology, (2005) Vol. 187, No. 3, pp. 419-427. .
Refs: 21
ISSN: 0022-0795 CODEN: JOENAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 003 Endocrinology
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Jan 2006
Last Updated on STN: 19 Jan 2006

L12 ANSWER 16 OF 59 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
TI Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1.
SO Biochemical and Biophysical Research Communications, (1 Apr 2005) Vol. 329, No. 1, pp. 386-390. .
Refs: 15
ISSN: 0006-291X CODEN: BBRCA
AU Katsuma S.; Hirasawa A.; Tsujimoto G.
AB Bile acids play essential roles in the absorption of dietary lipids and in the regulation of bile acid biosynthesis. Recently, a G protein-coupled receptor, TGR5, was identified as a cell-surface bile acid receptor. In this study, we show that bile acids promote glucagon-like peptide-1 (GLP-1) secretion through TGR5 in a murine enteroendocrine cell line STC-1. In STC-1 cells, bile acids promoted GLP-1 secretion in a dose-dependent manner. As STC-1 cells express TGR5 mRNA, we examined whether bile acids induce GLP-1 secretion through TGR5. RNA interference experiments showed that reduced expression of TGR5 resulted in reduced secretion of GLP-1. Furthermore, transient transfection of STC-1 cells with an expression plasmid containing TGR5 significantly enhanced GLP-1 secretion, indicating that bile acids promote GLP-1 secretion through TGR5 in STC-1 cells. Bile acids induced rapid and dose-dependent elevation of intracellular cAMP levels in STC-1 cells. An adenylate cyclase inhibitor, MDL12330A, significantly suppressed bile acid-promoted GLP-1 secretion, suggesting that bile acids induce GLP-1 secretion via intracellular cAMP production in STC-1 cells. .

ACCESSION NUMBER: 2005084016 EMBASE
TITLE: Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1.
AUTHOR: Katsuma S.; Hirasawa A.; Tsujimoto G.
CORPORATE SOURCE: G. Tsujimoto, Dept. of Genomic Drug Discov. Sci., Grad. Sch. of Pharmaceutical Sci., Kyoto University, 46-29 Yoshida Shimoadachi-cho, Sakyo-ku, Kyoto 606-8501, Japan. gtsuji@pharm.kyoto-u.ac.jp
SOURCE: Biochemical and Biophysical Research Communications, (1 Apr 2005) Vol. 329, No. 1, pp. 386-390. .
Refs: 15

ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2005
Last Updated on STN: 17 Mar 2005

L12 ANSWER 17 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN DUPLICATE 2
TI GLUTAMINYL BASED DP IV-INHIBITORS
INF Demuth; Hans-Ulrich, Halle/Saale, DE
Heiser; Ulrich, Halle/Saale, DE
Hoffmann; Matthias, Wengelsdorf, DE
Hoffmann; Torsten, Halle/Saale, DE
Niestroj; Andre J., Sennewitz, DE
Schilling; Stephan, Halle/Saale, DE
IN Demuth Hans-Ulrich (DE); Heiser Ulrich (DE); Hoffmann Matthias (DE); Hoffmann Torsten (DE); Niestroj Andre J (DE); Schilling Stephan (DE)
AB The present invention relates dipeptidyl peptidase IV inhibition and, more particularly, relates to glutaminyl derivatives, wherein the glutamin residue is bound in a peptide manner to a moiety which imitates the amino acid residue prolin, especially to a nitrogen containing moiety, pharmaceutical compositions containing said compounds, and the use of said compounds in inhibiting dipeptidyl peptidase IV and dipeptidyl peptidase IVlike enzyme activity.
CLMN 22
AN 10722598 IFIPAT;IFIUDB;IFICDB
TITLE: GLUTAMINYL BASED DP IV-INHIBITORS
INVENTOR(S): Demuth; Hans-Ulrich, Halle/Saale, DE
Heiser; Ulrich, Halle/Saale, DE
Hoffmann; Matthias, Wengelsdorf, DE
Hoffmann; Torsten, Halle/Saale, DE
Niestroj; Andre J., Sennewitz, DE
Schilling; Stephan, Halle/Saale, DE
PATENT ASSIGNEE(S): Unassigned
PATENT ASSIGNEE PROBABLE: Probiodrug DE (Probable)
AGENT: Brown Rudnick Berlack Israels LLP, One Financial Center, Box IP, Boston, MA, 02111, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004229848	A1	20041118
APPLICATION INFORMATION:	US 2004-839122		20040505

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2003-467914P	20030505 (Provisional)
	US 2003-468014P	20030505 (Provisional)
FAMILY INFORMATION:	US 2004229848	20041118

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 22

L12 ANSWER 18 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN DUPLICATE 3
TI METHOD OF PRODUCING INSULINOTROPIC GLP-1 (7-36) POLYPEPTIDE AND/ OR GLP-1 ANALOGS; TRANSFORMING AND FERMENTING GENE PRODUCTS FROM CELLS COMPRISING NUCLEOTIDE SEQUENCES CODING GLUCAGON LIKE POLYPEPTIDES FOR USE IN STIMULATION AND SECRETION OF INSULIN; DIABETES TREATMENT; BIOREACTORS
INF Sun; Yukun, Shanghai, CN

Wu; Aizhen, Shanghai, CN
Wu; Dengxi, Shanghai, CN
Yu; Gang, Shanghai, CN
Zhao; Shaoling, Shanghai, CN
Zhou; Jiaxiang, Shanghai, CN
Zhu; Zhiyong, Shanghai, CN

IN Sun Yukun (CN); Wu Aizhen (CN); Wu Dengxi (CN); Yu Gang (CN); Zhao Shaoling (CN); Zhou Jiaxiang (CN); Zhu Zhiyong (CN)

AB The present invention discloses a method of producing polypeptides, including insulinotropic GLP-1 (7-36) polypeptide and/or GLP-1 analogs, by ligating genes in a tandem way. Also disclosed are the recombinant polypeptides produced by such a method. Using the method of this invention, 1 to 32 copies of GLP-1 (7-36) and/or GLP-1 analog genes may be expressed in tandem and the desired polypeptide can be obtained after cleavage of a fusion protein and further processes of separation and purification thus making possible the production of recombinant polypeptides, including recombinant GLP-1(7-36) and/or GLP-1 analogs on a large scale, at a significantly reduced production cost.

CLMN 36 11 Figure(s).

FIG. 1 depicts the process to construct a expression vector containing one copy of the gene encoding GLP-1(7-36) polypeptide.

FIG. 2 shows the resulting DNA sequence encoding GLP-1 (7-36) polypeptide after ligation of fragments (1), (2), (3) and (4).

FIG. 3 shows the resulting DNA sequence encoding GLP-1 (7-36) polypeptide after ligation of fragments (1'), (2'), (3') and (4').

FIG. 4 depicts the process to construct a plasmid containing 2 to 32 copies of GLP-1(7-36) genes in tandem.

FIG. 5 shows the growth curve of genetically engineered bacterial cells during the process of fermentation.

FIG. 6 shows the HPLC analysis result of the recombinant GLP-1(736) polypeptide.

FIG. 7 shows the amino acid analysis results of the recombinant GLP-1(7-36) polypeptide.

FIG. 8 shows the mass spectrum analysis results of the recombinant GLP-1(7-36) polypeptide.

FIG. 9 shows the variation of the insulin concentration in the blood of mice after the mice were injected with GLP-1(7-36) polypeptide.

FIG. 10 shows the variation of the C-peptide concentration in the blood of mice after the mice were injected with GLP-1(7-36) polypeptide.

FIG. 11 shows the variation of the glucose concentration in the blood of mice after the mice were injected with GLP-1(7-36) polypeptide.

AN 10639757 IFIPAT;IFIUDB;IFICDB

TITLE: METHOD OF PRODUCING INSULINOTROPIC GLP-1 (7-36) POLYPEPTIDE AND/ OR GLP-1 ANALOGS; TRANSFORMING AND FERMENTING GENE PRODUCTS FROM CELLS COMPRISING NUCLEOTIDE SEQUENCES CODING GLUCAGON LIKE POLYPEPTIDES FOR USE IN STIMULATION AND SECRETION OF INSULIN; DIABETES TREATMENT; BIOREACTORS

INVENTOR(S): Sun; Yukun, Shanghai, CN
Wu; Aizhen, Shanghai, CN
Wu; Dengxi, Shanghai, CN
Yu; Gang, Shanghai, CN
Zhao; Shaoling, Shanghai, CN
Zhou; Jiaxiang, Shanghai, CN
Zhu; Zhiyong, Shanghai, CN

PATENT ASSIGNEE(S): Shanghai Hua-Yi Bio-Tech Lab

PATENT ASSIGNEE PROBABLE: Shanghai Hua Yi Bio Tech Lab CN (Probable)
AGENT: WONG, CABELLO, LUTSCH, RUTHERFORD & BRUCCULERI,;P.C., 20333 SH 249, SUITE 600, HOUSTON, TX, 77070, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004146985	A1	20040729
APPLICATION INFORMATION:	US 2004-761717		20040120

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION-IN-PART OF:	WO 2002-CN502	20020717	
FAMILY INFORMATION:	US 2004146985	20040729	

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION
OTHER SOURCE: CA 141:136205

PARENT CASE DATA:

This is a continuation-in-part of PCT/CN02/00502 which bears an international filing date of 17 Jul. 2002, and which claims the priority to Chinese Patent Application Serial No. 01126278.8 filed 19 Jul. 2001.

NUMBER OF CLAIMS: 36 11 Figure(s).
DESCRIPTION OF FIGURES:
FIG. 1 depicts the process to construct a expression vector containing one copy of the gene encoding GLP-1 (7-36) polypeptide.
FIG. 2 shows the resulting DNA sequence encoding GLP-1 (7-36) polypeptide after ligation of fragments (1), (2), (3) and (4).
FIG. 3 shows the resulting DNA sequence encoding GLP-1 (7-36) polypeptide after ligation of fragments (1'), (2'), (3') and (4').
FIG. 4 depicts the process to construct a plasmid containing 2 to 32 ***copies*** of GLP-1(7-36) genes in tandem.
FIG. 5 shows the growth curve of genetically engineered bacterial cells during the process of fermentation.
FIG. 6 shows the HPLC analysis result of the recombinant GLP-***1*** (736) polypeptide.
FIG. 7 shows the amino acid analysis results of the recombinant GLP-***1*** (7-36) polypeptide.
FIG. 8 shows the mass spectrum analysis results of the recombinant GLP -1(7-36) polypeptide.
FIG. 9 shows the variation of the insulin concentration in the blood of mice after the mice were injected with GLP-1(7-36) polypeptide.
FIG. 10 shows the variation of the C-peptide concentration in the blood of mice after the mice were injected with GLP-1(7-36) polypeptide.
FIG. 11 shows the variation of the glucose concentration in the blood of mice after the mice were injected with GLP-1(7-36) polypeptide.

L12 ANSWER 19 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI TREATMENT OF PATIENTS WITH MULTIPLE SCLEROSIS BASED ON GENE EXPRESSION CHANGES IN CENTRAL NERVOUS SYSTEM TISSUES; GENE MARKERS WHOSE EXPRESSION IS ALTERED IN MULTIPLE SCLEROSIS CAN BE USED TO DIAGNOSE OR PREDICT MS, AND CAN BE USED IN THE MONITORING OF THERAPIES; THESE GENES ALSO IDENTIFY THERAPEUTIC TARGETS
INF Dangond; Fernando, Newton, MA, US
Gullans; Steven R., Natick, MA, US
Hwang; Daehee, Seattle, WA, US
IN Dangond Fernando; Gullans Steven R; Hwang Daehee
AB The present invention identifies a number of gene markers whose expression is altered in multiple sclerosis (MS). These markers can be

used to diagnose or predict MS in subjects, and can be used in the monitoring of therapies. In addition, these genes identify therapeutic targets, the modification of which may prevent MS development or progression.

CLMN 56 2 Figure(s).

FIG. 1 Kernel density estimate based on five ratios.

FIGS. 2A & 2B Kernel density estimate and histogram of ratios with an adjusted bandwidth.

AN 10649595 IFIPAT;IFIUDB;IFICDB

TITLE: TREATMENT OF PATIENTS WITH MULTIPLE SCLEROSIS BASED ON GENE EXPRESSION CHANGES IN CENTRAL NERVOUS SYSTEM TISSUES; GENE MARKERS WHOSE EXPRESSION IS ALTERED IN MULTIPLE SCLEROSIS CAN BE USED TO DIAGNOSE OR PREDICT MS, AND CAN BE USED IN THE MONITORING OF THERAPIES; THESE GENES ALSO IDENTIFY THERAPEUTIC TARGETS

INVENTOR(S): Dangond; Fernando, Newton, MA, US
Gullans; Steven R., Natick, MA, US
Hwang; Daehee, Seattle, WA, US

PATENT ASSIGNEE(S): Unassigned

PATENT ASSIGNEE PROBABLE: Brigham and Women's Hospital (Probable)

AGENT: FULBRIGHT & JAWORSKI L.L.P.;SUITE 2400, 600 CONGRESS AVENUE, AUSTIN, TX, 78701-3271, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004156826	A1	20040812
APPLICATION INFORMATION:	US 2003-670766		20030925

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 2002-414219P	20020927 (Provisional)
FAMILY INFORMATION:	US 2004156826	20040812

DOCUMENT TYPE: Utility
Patent Application - First Publication

FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 56 2 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 Kernel density estimate based on five ratios.

FIGS. 2A & 2B Kernel density estimate and histogram of ratios with an adjusted bandwidth.

L12 ANSWER 20 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN

TI DERIVATIVES OF THE INSULINOTROPIC PEPTIDE EXENDIN-4 AND METHODS OF PRODUCTION THEREOF; RECOMBINANT METHODS;

INF Chen; Wen, Shanghai, CN
Sun; Yukun, Shanghai, CN
Wu; Dengxi, Shanghai, CN
Zhu; Zhiyong, Shanghai, CN

IN Chen Wen (CN); Sun Yukun (CN); Wu Dengxi (CN); Zhu Zhiyong (CN)

AB The present invention is directed to the development of novel exendin-4 derivatives exhibiting advantageous glucoseregulatory properties, and to methods of producing these derivatives, including recombinant methods in which these derivatives are produced by cleavage of a fusion protein containing multiple copies of the exendin-4 derivative peptide. The methods of the present invention can be used to simplify the process of producing the disclosed exendin-4 derivatives, thereby lowering the cost of their production.

CLMN 21 9 Figure(s).

FIG. 1 illustrates aligned amino acid sequences of GLP-1 (7-36) (SEQ ID NO:9), wild-type exendin-4 (SEQ ID NO: 1), and three inventive derivatives of wild-type exendin-4, namely, exendin-4 (Lys20, Arg40) (SEQ

ID NO:6), exendin-4 (His20, Arg40) (SEQ ID NO:7), and exendin-4 (Leu14, Lys20, Arg40) (SEQ ID NO:8). In this figure, shaded amino acids in the GLP-1 (7-36) and wildtype exendin-4 sequences indicates amino acids present in both sequences, while underlined amino acids in the three inventive derivatives of wild-type exendin-4 indicate substituted or added amino acids in these peptide sequences.

FIG. 2 shows the effects of saline control, GLP-1, wild-type exendin-4 ("ex-4 wt"), and the exendin-4 derivative exendin-4 (Leu14, Lys20, Arg40) ("ex-4 m") on the blood glucose levels of non-diabetic C57 BL/6J mice after glucose challenge.

FIG. 3 shows the effects of saline control, GLP-1, the exendin-4 derivative exendin-4 (Leu14, Lys20, Arg40) ("E4m") and the commercially available insulin Humalog (reg) on the blood glucose levels of db/db diabetic mice after glucose challenge.

FIG. 4 shows the long-term hypoglycemic effects of control, GLP1, and the exendin-4 derivative exendin-4 (Leu14, Lys20, Arg40) ("E4m") on the blood glucose levels of non-diabetic C57 BL/6J mice after a second glucose challenge. Vertical arrows indicate times of administration of glucose challenges.

FIG. 5 shows the peptide and corresponding DNA sequences used to construct the exendin-4 (Leu14, Lys20, Arg40) and exendin-4 (Lys20, Arg40) sequences. The peptide and corresponding DNA sequences used to construct the exendin-4 (Leu14, Lys20, Arg40) and the exendin-4 (Lys20, Arg40) sequences are shown in the top and bottom panels, respectively. The DNA sequence in the top panel is given in the sequence listing as SEQ ID NO:15, while the DNA sequence in the bottom panel is given in the sequence listing as SEQ ID NO:14. Restriction sites are as indicated; changed amino acid positions relative to the wild-type exendin4 sequence are in bold.

FIG. 6 shows the protocol described in Example 9 for the construction of the pUC8-EM4x1 vector containing one copy of the exendin-4 (Lys20, Arg40) of FIG. 5.

FIG. 7 shows the protocol described in Example 9 for the construction of the pUC8-EM4x2 vector containing two tandemly linked copies of the exendin-4 (Lys20, Arg40) of FIG. 5.

FIG. 8 shows the protocol described in Example 9 for the construction of the pUC8-EM4x4 vector containing four tandemly linked copies of the exendin-4 (Lys20, Arg40) of FIG. 5.

FIG. 9 shows the protocol described in Example 9 for the construction of the pUC8-EM4xN vector containing N tandemly linked copies of the exendin-4 (Lys20, Arg40) of FIG. 5.

AN	10635639 IFIPAT;IFIUDB;IFICDB
TITLE:	DERIVATIVES OF THE INSULINOTROPIC PEPTIDE EXENDIN-4 AND METHODS OF PRODUCTION THEREOF; RECOMBINANT METHODS;
INVENTOR(S):	Chen; Wen, Shanghai, CN Sun; Yukun, Shanghai, CN Wu; Dengxi, Shanghai, CN Zhu; Zhiyong, Shanghai, CN
PATENT ASSIGNEE(S):	Shanghai Huyai Bio-Lab Co., Ltd.
PATENT ASSIGNEE PROBABLE:	Shanghai Huyai Bio Lab Co Ltd CN (Probable)
AGENT:	David G. Rosenbaum, Esq.;Rosenbaum & Associates, P.C., Suite #380, 650 Dundee Road, Northbrook, IL, 60062, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2004142866	A1	20040722
APPLICATION INFORMATION:	US 2003-704409		20031107

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION-IN-PART OF:	WO 2002-CN316	20020508	

	NUMBER	DATE
PRIORITY APPLN. INFO.:	CN 2001-1128569	20010510
FAMILY INFORMATION:	US 2004142866	20040722
DOCUMENT TYPE:	Utility Patent Application - First Publication	
FILE SEGMENT:	CHEMICAL APPLICATION	
OTHER SOURCE:	CA 141:117136	

PARENT CASE DATA:

This application is a continuation-in-part of PCT/CN02/00316, which bears an international filing date of May 8, 2002, and which claims priority to Chinese Patent Application Serial No. 01112856.9, filed May 10, 2001.

NUMBER OF CLAIMS: 21 9 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1 illustrates aligned amino acid sequences of GLP-1 (7-36) (SEQ ID NO:9), wild-type exendin-4 (SEQ ID NO: 1), and three inventive derivatives of wild-type exendin-4, namely, exendin-4 (Lys20, Arg40) (SEQ ID NO:6), exendin-4 (His20, Arg40) (SEQ ID NO:7), and exendin-4 (Leu14, Lys20, Arg40) (SEQ ID NO:8). In this figure, shaded amino acids in the GLP-1 (7-36) and wildtype exendin-4 sequences indicates amino acids present in both sequences, while underlined amino acids in the three inventive derivatives of wild-type exendin-4 indicate substituted or added amino acids in these peptide sequences.

FIG. 2 shows the effects of saline control, GLP-1, wild-type exendin-4 ("ex-4 wt"), and the exendin-4 derivative exendin-4 (Leu14, Lys20, Arg40) ("ex-4 m") on the blood glucose levels of non-diabetic C57 BL/6J mice after glucose challenge.

FIG. 3 shows the effects of saline control, GLP-1, the exendin-4 derivative exendin-4 (Leu14, Lys20, Arg40) ("E4m") and the commercially available insulin Humalog (reg) on the blood glucose levels of db/db diabetic mice after glucose challenge.

FIG. 4 shows the long-term hypoglycemic effects of control, GLP1, and the exendin-4 derivative exendin-4 (Leu14, Lys20, Arg40) ("E4m") on the blood glucose levels of non-diabetic C57 BL/6J mice after a second glucose challenge. Vertical arrows indicate times of administration of glucose challenges.

FIG. 5 shows the peptide and corresponding DNA sequences used to construct the exendin-4 (Leu14, Lys20, Arg40) and exendin-4 (Lys20, Arg40) sequences. The peptide and corresponding DNA sequences used to construct the exendin-4 (Leu14, Lys20, Arg40) and the exendin-4 (Lys20, Arg40) sequences are shown in the top and bottom panels, respectively. The DNA sequence in the top panel is given in the sequence listing as SEQ ID NO:15, while the DNA sequence in the bottom panel is given in the sequence listing as SEQ ID NO:14. Restriction sites are as indicated; changed amino acid positions relative to the wild-type exendin4 sequence are in bold.

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FIG. 9 shows the protocol described in Example 9 for the construction of the pUC8-EM4xN vector containing N tandemly linked copies of the exendin-4 (Lys20, Arg40) of FIG. 5.

L12 ANSWER 21 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN

TI PEPTIDE COMPOSITIONS WITH EFFECTS ON CEREBRAL HEALTH; COGNITION ACTIVATORS; CENTRAL NERVOUS SYSTEM DISORDERS; ADMINISTERING ISOLATED

NUCLEIC ACID

INF Cao; Lei, Haddonfield, NJ, US
During; Matthew J., Philadelphia, PA, US
Haile; Colin N., Katy, TX, US
IN Cao Lei; During Matthew J; Haile Colin N

AB The present invention provides compositions and methods for ameliorating neurological or memory disorders and improving learning and cognition through the increase of cyclic AMP. Gilatides, peptides comprising the nine amino acid sequence (SEQ ID NO: 1), and functional analogs thereof are disclosed to modulate neurological activity when administered to a subject. The methods of the invention can be used to prevent or treat neurological disorders as well as improve memory retention and acquisition. The invention includes pharmaceutical compositions comprising a therapeutically or prophylactically effective amount of a Gilatide peptide or a functional analog thereof.

CLMN 32 37 Figure(s).

FIG. 1 is a bar graph of an ELISA of media from RINm5f cells for insulin confirming bioactivity of synthesized Gilatide peptide; Vehicle (*), GLP-1 (.squ.), GLP-1+
Exendin (9-39) (

FIG. 2 is a bar graph showing an increased mean latency to move into the dark compartment of a passive avoidance apparatus in which they had experienced an adverse stimulus of rats pretreated with 10 mu g Gilatide versus control (Vehicle (VEH) treated) at various time points following the initial adverse stimulus;

FIG. 3A is a bar graph showing that various doses of intracerebroventricular (i.c.v.) GLP-1 and Gilatide ((Ser(2))exendin(1-9)) enhanced latency in associative learning (passive avoidance), similar to vasopressin;

FIG. 3B is a bar graph showing that co-infusion of exendin (9-39) blocks the effects of GLP-1 and Gilatide ((Ser(2))exendin(1-9)) but not vasopressin;

FIGS. 4A is a graph showing no difference in acquisition between Gilatide treated and control groups based upon the results of a Morris Water Maze (MWM) task assay in which latency to find a submerged platform was measured;

FIG. 4B is a graph showing that 10 mu g, 30 mu g, and 60 mu g Gilatide facilitates retention for 48 hours of spatial learning in the Morris Water Maze task assay;

FIG. 5A is a graph of the distance traveled to find a hidden platform in the MWM following administration GLP-1, Gilatide ((Ser(2))exendin(1-9)) or control (Vehicle);

FIG. 5B is a graph demonstrating that both peptides GLP-1 and Gilatide decreased swimming speed compared to vehicle (P<0.05);

FIG. 6 depicts the representative swimming path tracings of five individual rats on day 5 in the MWM;

FIG. 7 is a bar graph showing mean (+-S.E.M.) latencies (acquisition) to move into the dark compartment from a bright compartment of a passive avoidance apparatus of rats pretreated via various routes of administration of Gilatide or Vehicle (VEH)+P=1.0; * P=<0.05, (t-test) vs. VEH;

FIG. 8 is a bar graph of mean (+-S.E.M.) latencies (retention) to move into the dark compartment from a bright compartment of a passive avoidance apparatus latency rats pretreated with various levels of Gilatide, Vehicle (VEH), or Nicotine, +P=0.1; * P<0.05, (t-test) vs. VEH, **P<0.05 vs. Nicotine;

FIG. 9A shows the enhancement of learning and memory by intranasal (Ser(2))exendin(1-9) where (Ser(2))exendin(1-9) (upslashed, 3, 10, and 30 mu g), but not GLP-1 (.squ.) enhanced latency in PA comparable to vasopressin (down-slashed, 0.3 mu g; +P=0.01 for (Ser(2))exendin(1-9) 3 mu g; *P<0.05 for (Ser(2))exendin(1-9) 10 mu g and vasopressin);

FIG. 9B shows that co-treatment with exendin (9-39) blocked the

effects of (Ser(2))exendin(1-9) (up slashed) but not vasopressin (down-slashed) (*P<0.05) resulting in effects similar in Exendin (9-39) only (dotted);

FIG. 10A is a graph showing that intranasal treatments of GLP-1, Gilatide, and Arecoline did not affect acquisition of spatial learning compared to the control;

FIG. 10B is a graph showing that (Ser(2))exendin(1-9) (up slashed, 30 mu g) enhanced retention of spatial learning, comparable to arecoline (wavy lined, 0.3 mg s.c.;**P<0.01), over that of vehicle (*) or GLP-1 (.squ.);

FIG. 11 is a graph showing the effects of (Ser(2))exendin(1-9) (up slashed, 10 mu g), arecoline (wavy, 0.3 mg) and vasopressin (down-slashed, 0.3 mu g) on repeated testing in PA in which (Ser(2))exendin(1-9) enhanced retention to a greater degree than arecoline (wavy) and vasopressin (down slashed) (*P<0.05);

FIG. 12A is a bar graph illustrating that acute administration of Gilatide has no significant effect on food intake of rats following 18 hours of deprivation;

FIG. 12B is a bar graph illustrating that acute administration of Gilatide has no significant effect on water intake of rats following 18 hours of deprivation;

FIG. 13 is a bar graph showing the effects of Gilatide on consolidation of learning for rats treated intranasally with 10 mu g/kg Gilatide 20 minutes (TRN-TXT, grey) or 24 hours (TXTDYL-TRN, black) after the conditioning session;

FIG. 14 is a bar graph of latency, measured in a passive avoidance apparatus, for rats pretreated with various levels of Gilatide with or without an Exendin-4 antagonist, or vehicle (VEH) illustrating that co-treatment with the Exendin-4 antagonist (9-39) (10 mu g) completely blocked enhancement of associative learning by Gilatide (10 mu g) (*P=0.03 vs. Gilatide 10 mu g, combination vs. VEH, ##P=0.43) and increasing the dose of Gilatide (20 mu g) surmounted the antagonism (vs. VEH, **P=0.04);

FIG. 15 is a bar graph of mean latencies measured in a passive avoidance apparatus for rats pretreated with Gilatide, saline, scrambled peptide, or vehicle (VEH);

FIG. 16 is a bar graph of % control latency versus dose of intranasal administration of Gilatide ((Ser(2))exendin(1-9)) in GLP-1R+/+ (*) and GLP-1R-/-(.squ.) mice demonstrating that Gilatide enhanced latency times in GLP-1R+/+ (*P<0.05) but not in GLP-1R-/-mice in the PA paradigm;

FIG. 17 is a bar graph of % freezing behavior demonstrating contextual fear conditioning in which GLP-1R-/-(.squ.) (**P<0.01) showed significant decrements in contextual fear conditioning compared to GLP-1R+/+ mice (*);

FIG. 18A is a graph demonstrating that Gilatide ((Ser(2))exendin (1-9)) (1 mu g, slashed circles) produced a trend towards a decrease in latency compared to vehicle-treated mice (*) in acquisition of spatial learning in wild type mice (F=2. 72(1,72); P=0.10);

FIG. 18B is a bar graph demonstrating that Gilatide ((Ser(2)) exendin(1-9)) at doses of 1 mu g (slashed box) and 3 mu g (

FIG. 19A is a graph demonstrating that Gilatide ((Ser(2))exendin (1-9)) (slashed circles) did not enhance acquisition in GLP-1R-/-mice compared to vehicle (*);

FIG. 19B is a bar graph demonstrating no difference in latency to find a visual platform for wild-type (*) and GLP-1R-/-mice (.squ.);

FIG. 20 is a bar graph demonstrating that that Gilatide ((Ser(2)) exendin(1-9)) at doses of 1 mu g (slashed box) and 3 mu g (

FIG. 21 is a graph showing the decreased distance traveled to locate the hidden platform in rats with over-expression of GLP1R in hippocampus (rAAV) (.xcirc.) compared to EGFP controls (*);

FIG. 22 is a bar graph demonstrating that GLP-1R overexpression (.squ.), and arecoline (*P<0.05) (

FIG. 23 is a bar graph showing no effect of Gilatide on locomotor activity

of rats where mean (+-S.E.M.) distance traveled (cm) was measured over 30 minutes in rats administered VEH (5% beta cyclodextrin) or Gilatide (10-60 mu g, intranasal, in 5% beta cyclodextrin);

FIG. 24 is a bar graph illustrating the effects of Gilatide on nociception based upon the results of a tail immersion assay where mean (+-S.E.M.) tail flick latencies following pretreatment with VEH (5% beta cyclodextrin) or Gilatide (10-60 mu g, intranasal, in 5% % cyclodextrin) was measured;

FIG. 25A is a graph showing that intranasal Gilatide (slashed) enhanced MAP kinase immunoreactivity in the cytosolic fraction of the hippocampus of rats compated to vehicle (*),*P=0.05;

FIG. 25B is a graph showing that intranasal Gilatide (slashed) enhanced MAP kinase immunoreactivity in the nuclear fraction of the hippocampus of rats compated to vehicle (*); *P=0.05;

FIG. 26 is a bar graph demonstrating that the effects of intranasal Gilatide on associative learning in rats was blocked by administration of a specific MEK inhibitor, PD98059 (5 mu g, i.c.v.), post-training (slashed), but not pre-training (L);

FIG. 27 is a bar graph showing that the latency to seizure onset in response to 20 mg/kg kainic acid (KA) was significantly lower (*P<0.05) in GLP-1-/-(.squ.) compared to wild-type GLP1+/+ mice (*); and

FIG. 28 is a bar graph showing that the maximum seizure severity score was greater in GLP-1-/-mice (.squ.) compared to wildtype GLP-1+/+ mice (*).

AN	10585210 IFIPAT;IFIUDB;IFICDB			
TITLE:	PEPTIDE COMPOSITIONS WITH EFFECTS ON CEREBRAL HEALTH; COGNITION ACTIVATORS; CENTRAL NERVOUS SYSTEM DISORDERS; ADMINISTERING ISOLATED NUCLEIC ACID			
INVENTOR(S):	Cao; Lei, Haddonfield, NJ, US During; Matthew J., Philadelphia, PA, US Haile; Colin N., Katy, TX, US			
PATENT ASSIGNEE(S):	THOMAS JEFFERSON UNIVERSITY, Philadelphia, PA, US			
AGENT:	NUTTER MCCLENNEN & FISH LLP, WORLD TRADE CENTER WEST, 155 SEAPORT BOULEVARD, BOSTON, MA, 02210-2604, US			
	NUMBER	PK	DATE	
PATENT INFORMATION:	US 2004092432	A1	20040513	
APPLICATION INFORMATION:	US 2003-405090		20030401	
	APPLN. NUMBER		DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION-IN-PART OF:	US 2001-939472		20010824	PENDING
	NUMBER		DATE	
PRIORITY APPLN. INFO.:	US 2000-227631P		20000824	(Provisional)
	US 2002-369249P		20020401	(Provisional)
FAMILY INFORMATION:	US 2004092432		20040513	
DOCUMENT TYPE:	Utility Patent Application - First Publication			
FILE SEGMENT:	CHEMICAL APPLICATION			
OTHER SOURCE:	CA 140:395534			
NUMBER OF CLAIMS:	32 37 Figure(s).			

DESCRIPTION OF FIGURES:

FIG. 1 is a bar graph of an ELISA of media from RINm5f cells for insulin confirming bioactivity of synthesized Gilatide peptide; Vehicle (*), ***GLP*** -1 (.squ.), GLP-1+Exendin (9-39) (

FIG. 2 is a bar graph showing an increased mean latency to move into the dark

compartment of a passive avoidance apparatus in which they had experienced an adverse stimulus of rats pretreated with 10 mu g Gilatide versus control (Vehicle (VEH) treated) at various time points following the initial adverse stimulus;
FIG. 3A is a bar graph showing that various doses of intracerebroventricular (i.c.v.) GLP-1 and Gilatide ((Ser(2))exendin (1-9)) enhanced latency in associative learning (passive avoidance), similar to vasopressin;
FIG. 3B is a bar graph showing that co-infusion of exendin (9-39) blocks the effects of GLP-1 and Gilatide ((Ser(2)) ***exendin*** (1-9)) but not vasopressin;
FIGS. 4A is a graph showing no difference in acquisition between Gilatide treated and control groups based upon the results of a Morris Water Maze (MWM) task assay in which latency to find a submerged platform was measured;
FIG. 4B is a graph showing that 10 mu g, 30 mu g, and 60 mu g Gilatide facilitates retention for 48 hours of spatial learning in the Morris Water Maze task assay;
FIG. 5A is a graph of the distance traveled to find a hidden platform in the MWM following administration GLP-1, Gilatide ((Ser(2)) ***exendin*** (1-9)) or control (Vehicle);
FIG. 5B is a graph demonstrating that both peptides GLP-1 and Gilatide decreased swimming speed compared to vehicle ($P<0.05$);
FIG. 6 depicts the representative swimming path tracings of five individual rats on day 5 in the MWM;
FIG. 7 is a bar graph showing mean (+-S.E.M.) latencies (acquisition) to move into the dark compartment from a bright compartment of a passive avoidance apparatus of rats pretreated via various routes of administration of Gilatide or Vehicle (VEH)+P=1.0; * P=<0.05, (t-test) vs. VEH;
FIG. 8 is a bar graph of mean (+-S.E.M.) latencies (retention) to move into the dark compartment from a bright compartment of a passive avoidance apparatus latency rats pretreated with various levels of Gilatide, Vehicle (VEH), or Nicotine, +P=0.1; * $P<0.05$, (t-test) vs. VEH, **$P<0.05$ vs. Nicotine;
FIG. 9A shows the enhancement of learning and memory by intranasal (Ser(2)) ***exendin*** (1-9) where (Ser(2))exendin(1-9) (upslashed, 3, 10, and 30 mu g), but not GLP-1 (.squ.) enhanced latency in PA comparable to vasopressin (down-slashed, 0.3 mu g; +P=0.01 for (Ser(2)) ***exendin*** (1-9) 3 mu g; *$P<0.05$ for (Ser(2))exendin(1-9) 10 mu g and vasopressin);
FIG. 9B shows that co-treatment with exendin (9-39) blocked the effects of (Ser(2))exendin(1-9) (up slashed) but not vasopressin (down-slashed) (*$P<0.05$) resulting in effects similar in Exendin (9-39) only (dotted);
FIG. 10A is a graph showing that intranasal treatments of GLP-***1*** , Gilatide, and Arecoline did not affect acquisition of spatial learning compared to the control;
FIG. 10B is a graph showing that (Ser(2))exendin(1-9) (up slashed, 30 mu g) enhanced retention of spatial learning, comparable to arecoline (wavy lined, 0.3 mg s.c.;**$P<0.01$), over that of vehicle (*) or GLP-***1*** (.squ.);
FIG. 11 is a graph showing the effects of (Ser(2))exendin(1-9) (up slashed, 10 mu g), arecoline (wavy, 0.3 mg) and vasopressin (down-slashed, 0.3 mu g) on repeated testing in PA in which (Ser(2))exendin (1-9) enhanced retention to a greater degree than arecoline (wavy) and vasopressin (down slashed) (*$P<0.05$);
FIG. 12A is a bar graph illustrating that acute administration of Gilatide has no significant effect on food intake of rats following 18 hours of deprivation;
FIG. 12B is a bar graph illustrating that acute administration of Gilatide has no significant effect on water intake of rats following 18 hours of deprivation;
FIG. 13 is a bar graph showing the effects of Gilatide on consolidation of learning for rats treated intranasally with 10 mu g/kg Gilatide 20 minutes (TRN-TXT, grey) or 24 hours (TXTDYL-TRN, black) after the conditioning session;
FIG. 14 is a bar graph of latency, measured in a passive avoidance apparatus, for rats pretreated with various levels of Gilatide with or without an

Exendin -4 antagonist, or vehicle (VEH) illustrating that co-treatment with the Exendin-4 antagonist (9-39) (10 mu g) completely blocked enhancement of associative learning by Gilatide (10 mu g) (*P=0.03 vs. Gilatide 10 mu g, combination vs. VEH, ##P=0.43) and increasing the dose of Gilatide (20 mu g) surmounted the antagonism (vs. VEH, **P=0.04);
FIG. 15 is a bar graph of mean latencies measured in a passive avoidance apparatus for rats pretreated with Gilatide, saline, scrambled peptide, or vehicle (VEH);
FIG. 16 is a bar graph of % control latency versus dose of intranasal administration of Gilatide ((Ser(2))exendin(1-9)) in GLP-1R+/+ (*) and GLP-1R-/-(.squ.) mice demonstrating that Gilatide enhanced latency times in GLP-1R+/+ (*P<0.05) but not in GLP-1R-/-mice in the PA paradigm;
FIG. 17 is a bar graph of % freezing behavior demonstrating contextual fear conditioning in which GLP-1R-/-(.squ.) (**P<0.01) showed significant decrements in contextual fear conditioning compared to GLP-1R+/+ mice (*);
FIG. 18A is a graph demonstrating that Gilatide ((Ser(2))exendin (1-9)) (1 mu g, slashed circles) produced a trend towards a decrease in latency compared to vehicle-treated mice (*) in acquisition of spatial learning in wild type mice (F=2. 72(1,72); P=0.10);
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FIG. 19B is a bar graph demonstrating no difference in latency to find a visual platform for wild-type (*) and GLP-1R-/-mice (.squ.);
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FIG. 21 is a graph showing the decreased distance traveled to locate the hidden platform in rats with over-expression of GLP1R in hippocampus (rAAV) (.xcirc.) compared to EGFP controls (*);
FIG. 22 is a bar graph demonstrating that GLP-1R overexpression (.squ.), and arecoline (*P<0.05) (
FIG. 23 is a bar graph showing no effect of Gilatide on locomotor activity of rats where mean (+-S.E.M.) distance traveled (cm) was measured over 30 minutes in rats administered VEH (5% beta cyclodextrin) or Gilatide (10-60 mu g, intranasal, in 5% beta cyclodextrin);
FIG. 24 is a bar graph illustrating the effects of Gilatide on nociception based upon the results of a tail immersion assay where mean (+-S.E.M.) tail flick latencies following pretreatment with VEH (5% beta cyclodextrin) or Gilatide (10-60 mu g, intranasal, in 5% % cyclodextrin) was measured;
FIG. 25A is a graph showing that intranasal Gilatide (slashed) enhanced MAP kinase immunoreactivity in the cytosolic fraction of the hippocampus of rats compated to vehicle (*),*P=0.05;
FIG. 25B is a graph showing that intranasal Gilatide (slashed) enhanced MAP kinase immunoreactivity in the nuclear fraction of the hippocampus of rats compated to vehicle (*); *P=0.05;
FIG. 26 is a bar graph demonstrating that the effects of intranasal Gilatide on associative learning in rats was blocked by administration of a specific MEK inhibitor, PD98059 (5 mu g, i.c.v.), post-training (slashed), but not pre-training (L);
FIG. 27 is a bar graph showing that the latency to seizure onset in response to 20 mg/kg kainic acid (KA) was significantly lower (*P<0.05) in GLP-***1*** -/-(.squ.) compared to wild-type GLP1+/+ mice (*); and
FIG. 28 is a bar graph showing that the maximum seizure severity score was greater in GLP-1-/-mice (.squ.) compared to wildtype ***GLP*** -1+/+ mice (*).

L12 ANSWER 22 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI THERAPEUTIC AND DIAGNOSTIC METHODS AND COMPOSITIONS BASED ON JAGGED/NOTCH PROTEINS AND NUCLEIC ACIDS; THE ADDITION OR INCREASED EXPRESSION OF JAGGED DECREASES THE MIGRATION AND INVASION OF MICROVASCULAR CELLS FROM THE VASO VASORUM, AND INCREASES OR STIMULATES THE MIGRATION OF LARGE VESSEL ENDOTHELIAL CELLS.

INF Maciag; Thomas, Freeport, ME
Prudovsky; Igor A., Old Orchard Beach, ME
Small; Deena J., Scarborough, ME
Zimrin; Ann B., Baltimore, MD

IN Maciag Thomas; Prudovsky Igor A; Small Deena J; Zimrin Ann B

AB This invention relates to therapeutic and diagnostic methods and compositions based on Jagged/Notch proteins and nucleic acids, and on their role in the signaling pathway relating to endothelial cell migration and/or differentiation. In addition, this invention provides a substantially purified Jagged protein, as well as a substantially purified nucleic acid or segment thereof encoding Jagged protein, or a functionally equivalent derivative, or allelic or species variant thereof. Further, this invention provides a substantially purified soluble Jagged protein and a substantially purified nucleic acid encoding same as well as a recombinant cell comprising a nucleic acid encoding a soluble Jagged protein. Soluble Jagged provides further therapeutic and diagnostic methods relating to diseases, disorders, and conditions involving Jagged/Notch signaling including, inter alia, angiogenesis, differentiation, and control of gene expression.

CLMN 11

GI 18 Drawing Sheet(s), 24 Figure(s).

FIG. 1 is a diagram illustrating the phenotypic alterations of HUVEC by cytokines. Early studies demonstrated that HUVEC populations are able to generate capillary-like, lumencontaining structures when introduced into a growth-limited environment in vitro. However, exposure of an HUVEC population to polypeptide cytokines, such as IL-1 and IFN gamma, as inducers of HUVEC differentiation in vitro, led to an understanding that the precursor form of IL-1 alpha was responsible for the induction of HUVEC senescence in vitro, the only truly terminal HUVEC phenotype identified to date. (PD=population doubling).

FIG. 2 is a diagram illustrating the domain structure of the Notch ligand family. (Numbers refer to the number of EGF repeats in the extracellular domain.) As indicated in this chart, although the intracellular domain of the Jagged gene contains a sequence with no known homology to intracellular regions of other transmembrane structures, the extracellular region of the gene contains a cys-rich region, 16 epidermal growth factor (EGF) repeats, and a Delta-Serrate-Lag (DSL) domain, typical of comparable regions found in other genes including the Drosophila ligands, Serrate and Delta, and the C. elegans genes, Apx-1 and Lag-2.

FIG. 3 is a diagram illustrating the Notch signaling pathway. The components of the Notch signaling pathway are illustrated, using the myoblast as an example. The Notch signaling pathway, when activated by Jagged in the endothelial cell, involves cleavage of the intracellular domain by a protease, nuclear trafficking of the Notch fragment and the interaction of this fragment with the KBF2/RBP-Jk transcription factor, a homolog of the Drosophila Suppressor of Hairless (Su(H)) gene, which is a basic helix-loop-helix transcription factor involved in Notch signaling.

FIG. 4 is a diagram illustrating the domain structure of the Notch receptor family. (Numbers refer to the number of EGF repeats in the extracellular domain.) As indicated in this chart, in addition to the 36 EGF repeats within the extracellular domain of Notch 1, there is a cys-rich domain composed of three Notch-Lin-Glp (NLG) repeats, followed by a cys-poor region between the transmembrane and NLG domain. The intracellular domain of Notch 1 contains six ankyrin/Cdc10 repeats positioned between two nuclear localization sequences (NLS). In the carboxy-terminal direction from this region is a polyglutamine-rich domain (OPA) and a pro-glu-ser-thr (PEST) domain (SEQ ID NO:33): Comparable structures are shown for Lin12 and Glp-1.

FIG. 5 is an image of a gel depicting the RT-PCR analysis of steady-state levels of Jagged, Notch I and Notch 2 transcripts in HUVEC. Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as a positive control.

FIG. 6 is a graph depicting the effect of the Jagged antisense oligonucleotide (JAS) (5'-TGGGGACCGCATCGCTGC-3' (SEQ ID NO:29)) on BMEC sprout formation, as compared with the effect on three control oligomers, a Jagged sense oligonucleotide (JS) (5'GCAGCGATGCGGTCCCCA-3' (SEQ ID NO:30)), a 3' antisense Jagged oligomer (3' AS) (5'-GAATCAAGGCTCCCCTAG-3' (SEQ ID NO:31)), and a mutated 5' antisense Jagged (MUT5' AS) oligomer (5'TGCGGTCCCCAACGGTGG-3' (SEQ ID NO:32)).

FIG. 7A is a graph depicting the effect of the antisense Jagged oligonucleotide on bovine microvascular endothelial cells (BMEC) .

FIG. 7B is a graph depicting the effect of the antisense Jagged oligonucleotide on bovine aorta endothelial cells (BAEC).

FIG. 8A is a diagram depicting the amino acid sequence of human Jagged (GenBank Accession No. U77720 (SEQ ID NO:1)). The amino acid sequence, which is depicted using the standard one-letter amino acid residue code, is provided. The amino acid sequence comprises various domains including, but not limited to, a signal peptide (from about amino acid residue 1 to about amino acid residue 21); a DSL domain (from about amino acid residue 185 to about amino acid residue 229); EGF repeats (from about amino acid residue 234 to about amino acid residue 862); a cysteine-rich region (from about amino acid residue 863 to about amino acid residue 1002); a transmembrane domain (from about amino acid residue 1068 to about amino acid residue 1093) ; and a cytoplasmic region (from about amino acid residue 1094 to about amino acid residue 1218).

FIGS. 8B-C is a diagram depicting the nucleic acid sequence of human Jagged (GenBank Acc. No. U77720 (SEQ ID NO:2)). Nucleotides designated by "Y" indicates C or T at that position, and nucleotides designated by "R" indicates G or A.

FIG. 9 is an image depicting an immunoblot analysis of murine pro-alpha-1(I) collagen expression in insert-less vector and soluble Jagged-1 NIH 3T3 cell transfectants. Cell lysates were prepared from pMexNeo insert-less vector control NIH 3T3 cell transfectants (lane 1), and soluble Jagged-1 NIH 3T3 transfectant clones 38-1 (lane 2) and 38-4 (lane 3). The proteins were transferred to Hybond C membranes and the blots were immunostained using SP1.D8 monoclonal antibody specific for the pro-alpha-1(I) collagen amino-terminal extension peptide as described elsewhere herein.

FIG. 10A is an image depicting the growth of control empty vector -transfected NIH 3T3 cells on plastic. Empty vectortransfected control NIH 3T3 cells were plated at 2 x 104 cells per cm2 on cell culture plastic. Two days after plating, the empty vector -transfected NIH 3T3 cells on plastic did not form multicellular chords. (Phase contrast at a magnification of 100 x).

FIG. 10B is an image depicting formation of multicellular chords of soluble Jagged-1 transfected NIH 3T3 cells on plastic. Soluble Jagged-1 transfected NIH 3T3 cells were plated at 2 x 104 cells per cm2 on cell culture plastic. Two days after plating, the soluble Jagged-1 transfectants formed multicellular chords on plastic. (Phase contrast at a magnification of 100 x).

FIG. 10C is an image depicting growth of control empty vectortransfected NIH 3T3 cells on collagen. Empty vector -transfected control NIH 3T3 cells were plated at 2 x 104 cells per cm2 on collagen. Two days after plating, the empty vector -transfected control NIH 3T3 cells did not form multicellular chords on collagen. (Phase contrast at a magnification of 100 x).

FIG. 10D is an image depicting formation of chords by soluble Jagged-1 transfected NIH 3T3 cells grown on collagen. Soluble Jagged-1 transfected NIH 3T3 cells were plated at 2 x 104 cells per cm2 on collagen. Two days after plating, the soluble Jagged1 transfectants formed multicellular chords on both plastic (FIG. 10B, supra) and on collagen. (Phase contrast at a magnification of 100 x).

FIG. 11 is a graph depicting the growth kinetics of soluble Jagged-1 and control insert-less vector NIH 3T3 cell transfectants. The cells were plated at a seed density of 1 x 104 cells per cm2 and the cell numbers were assessed daily in quadruplicate via hemocytometer count.

Both insert-less vector and soluble Jagged-1 cell populations reached confluence at approximately 4 days after plating. The data disclosed are the mean+-standard error of the mean.

FIG. 12A is an image depicting the angiogenesis present in tissues of nude mice injected with soluble Jagged-1 transfected NIH 3T3 cells. The image depicts soluble Jagged-1 tissue mass formation in nude mice. The image depicts a deep dermal view of a soluble Jagged-1 NIH 3T3 cell tissue mass 10 weeks after intradermal injection of the cell transfectants into the flank of a nude mouse. The data disclosed demonstrate prominent angiogenesis and arborizing microvessels over the deep surface.

FIG. 12B is an image depicting the angiogenesis present in tissues of nude mice injected with soluble Jagged-1 transfected NIH 3T3 cells. The image depicts hematoxylin and eosin staining of a paraffin section of the soluble Jagged-1 tissue mass depicted in FIG. 12A. The image depicts prominent surface bloodfilled capillaries, penetrating vessels, and intra-tumor blood islands. Magnification is 100 x .

FIG. 12C is an image depicting the immunohistochemical analysis of tissues of nude mice injected with soluble Jagged-1 transfected NIH 3T3 cells using anti-CD31 (PECAM) antibody. The image depicts a low magnification (100 x) view of a frozen section of the tissue mass depicted in FIG. 12A demonstrating the immunohistochemical localization of CD31 (PECAM). The image depicts two cross sections of a microvessel along with a high density of CD31 positivity.

FIG. 12D is an image depicting the immunohistochemical analysis of tissues of nude mice injected with soluble Jagged-1 transfected NIH 3T3 cells using anti-CD31 (PECAM) antibody. The image depicts a higher magnification (500 x) of the view of a frozen section of the tissue mass which is depicted at a magnification of 100 x in FIG. 12C. The data disclosed herein demonstrate that immunohistochemical localization of CD31 is comprised of groups of single cells or angulated collection of CD31-positive cells.

FIG. 13A is an image depicting the amino acid sequence of soluble-Jagged (SEQ ID NO:18).

FIGS. 13B-C is an image depicting the nucleic acid sequence of soluble-Jagged (SEQ ID NO:17). Nucleotides designated by "Y" indicates C or T at that position, and nucleotides designated by "R" indicates G or A.

AN	04045993 IFIPAT;IFIUDB;IFICDB
TITLE:	THERAPEUTIC AND DIAGNOSTIC METHODS AND COMPOSITIONS BASED ON JAGGED/NOTCH PROTEINS AND NUCLEIC ACIDS; THE ADDITION OR INCREASED EXPRESSION OF JAGGED DECREASES THE MIGRATION AND INVASION OF MICROVASCULAR CELLS FROM THE VASO VASORUM, AND INCREASES OR STIMULATES THE MIGRATION OF LARGE VESSEL ENDOTHELIAL CELLS.
INVENTOR(S):	Maciag; Thomas, Freeport, ME Prudovsky; Igor A., Old Orchard Beach, ME Small; Deena J., Scarborough, ME Zimrin; Ann B., Baltimore, MD
PATENT ASSIGNEE(S):	Maine Medical Center Research Institute, Scarborough, ME, US
PRIMARY EXAMINER:	Nolan, Patrick J
ASSISTANT EXAMINER:	DeCloux, Amy
AGENT:	Morgan, Lewis & Bockius, LLP

	NUMBER	PK	DATE
PATENT INFORMATION:	US 6716974	B1	20040406
APPLICATION INFORMATION:	US 2000-579536		20000524
EXPIRATION DATE:	30 May 2017		

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	WO 1997-US9407	19970530	PENDING

CONTINUATION-IN-PART OF: US 1998-199865 19981125 6433138

	NUMBER	DATE
PRIORITY APPLN. INFO.:	US 1996-18841P	19960531 (Provisional)
FAMILY INFORMATION:	US 6716974	20040406
	US 6433138	
DOCUMENT TYPE:	Utility	
	Granted Patent - Utility, no Pre-Grant Publication	
FILE SEGMENT:	CHEMICAL	
	GRANTED	
OTHER SOURCE:	CA 140:321722	

GOVERNMENT INTEREST:
This invention was supported in part by funds from the U.S. Government (National Institutes of Health Grant Nos. AG07450-12, HL32348-18, HL54710-04, and HL35627-16) and the U.S. Government may therefore have certain rights in the invention.

PARENT CASE DATA:

The present application is a continuation-in-part of U.S. application Ser. No. 09/199,865, now U.S. Pat. No. 6,433,138 filed on Nov. 25, 1998, which is a continuation of PCT Application No. US/PCT97/09407, filed on May 30, 1997, all of which are entitled to priority under 35 U.S.C. section 119(e), to U.S. Provisional Application No. 60/018,841, filed on May 31, 1996, and all of which are hereby incorporated herein by reference in their entirety.

MICROFILM REEL NO: 011142 FRAME NO: 0814
NUMBER OF CLAIMS: 11
GRAPHICS INFORMATION: 18 Drawing Sheet(s), 24 Figure(s).
DESCRIPTION OF FIGURES:
FIG. 1 is a diagram illustrating the phenotypic alterations of HUVEC by cytokines. Early studies demonstrated that HUVEC populations are able to generate capillary-like, lumencontaining structures when introduced into a growth-limited environment in vitro. However, exposure of an HUVEC population to polypeptide cytokines, such as IL-1 and IFN gamma, as inducers of HUVEC differentiation in vitro, led to an understanding that the precursor form of IL-1 alpha was responsible for the induction of HUVEC senescence in vitro, the only truly terminal HUVEC phenotype identified to date. (PD=population doubling).
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domain of Notch 1 contains six ankyrin/Cdc10 repeats positioned between two nuclear localization sequences (NLS). In the carboxy-terminal direction from this region is a polyglutamine-rich domain (OPA) and a pro-glu-ser-thr (PEST) domain (SEQ ID NO:33): Comparable structures are shown for Lin12 and Glp-1.

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FIG. 8A is a diagram depicting the amino acid sequence of human Jagged (GenBank Accession No. U77720 (SEQ ID NO:1)). The amino acid sequence, which is depicted using the standard one-letter amino acid residue code, is provided. The amino acid sequence comprises various domains including, but not limited to, a signal peptide (from about amino acid residue 1 to about amino acid residue 21); a DSL domain (from about amino acid residue 185 to about amino acid residue 229); EGF ***repeats*** (from about amino acid residue 234 to about amino acid residue 862); a cysteine-rich region (from about amino acid residue 863 to about amino acid residue 1002); a transmembrane domain (from about amino acid residue 1068 to about amino acid residue 1093) ; and a cytoplasmic region (from about amino acid residue 1094 to about amino acid residue 1218).

FIGS. 8B-C is a diagram depicting the nucleic acid sequence of human Jagged (GenBank Acc. No. U77720 (SEQ ID NO:2)). Nucleotides designated by "Y" indicates C or T at that position, and nucleotides designated by "R" indicates G or A.

FIG. 9 is an image depicting an immunoblot analysis of murine pro-alpha-1(I) collagen expression in insert-less vector and soluble Jagged-1 NIH 3T3 cell transfectants. Cell lysates were prepared from pMexNeo insert-less vector control NIH 3T3 cell transfectants (lane 1), and soluble Jagged-1 NIH 3T3 transfectant clones 38-1 (lane 2) and 38-4 (lane 3). The proteins were transferred to Hybond C membranes and the blots were immunostained using SP1.D8 monoclonal antibody specific for the pro-alpha-1(I) collagen amino-terminal extension peptide as described elsewhere herein.

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FIG. 10C is an image depicting growth of control empty ***vectortransfected*** NIH 3T3 cells on collagen. Empty vector -transfected control NIH 3T3 cells were plated at 2 x 104 cells per cm2 on collagen. Two days after plating, the empty vector-transfected control NIH 3T3 cells did not form multicellular chords on collagen. (Phase contrast at a magnification of 100 x).

FIG. 10D is an image depicting formation of chords by soluble Jagged-1 transfected NIH 3T3 cells grown on collagen. Soluble Jagged-1 transfected NIH 3T3 cells were plated at 2 x 104 cells per cm2 on collagen. Two days after plating, the soluble Jagged1 transfectants formed multicellular chords on both

plastic (FIG. 10B, supra) and on collagen. (Phase contrast at a magnification of 100 x).
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FIG. 12A is an image depicting the angiogenesis present in tissues of nude mice injected with soluble Jagged-1 transfected NIH 3T3 cells. The image depicts soluble Jagged-1 tissue mass formation in nude mice. The image depicts a deep dermal view of a soluble Jagged-1 NIH 3T3 cell tissue mass 10 weeks after intradermal injection of the cell transfectants into the flank of a nude mouse. The data disclosed demonstrate prominent angiogenesis and arborizing microvessels over the deep surface.
FIG. 12B is an image depicting the angiogenesis present in tissues of nude mice injected with soluble Jagged-1 transfected NIH 3T3 cells. The image depicts hematoxylin and eosin staining of a paraffin section of the soluble Jagged-1 tissue mass depicted in FIG. 12A. The image depicts prominent surface bloodfilled capillaries, penetrating vessels, and intra-tumor blood islands. Magnification is 100 x .
FIG. 12C is an image depicting the immunohistochemical analysis of tissues of nude mice injected with soluble Jagged-1 transfected NIH 3T3 cells using anti-CD31 (PECAM) antibody. The image depicts a low magnification (100 x) view of a frozen section of the tissue mass depicted in FIG. 12A demonstrating the immunohistochemical localization of CD31 (PECAM). The image depicts two cross sections of a microvessel along with a high density of CD31 positivity.
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L12 ANSWER 23 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI New glutamine derivatives used for treating e.g. non-insulin dependent diabetes mellitus, obesity, atherosclerosis, inflammatory bowel disease and neurodegenerative diseases.
IN DEMUTH, H; HEISER, U; HOFFMANN, M; HOFFMANN, T; NIESTROJ, A; SCHILLING, S; NIESTROJ, A J
AN 2004-833676 [82] WPIDS
CR 2004-805062 [79]; 2004-813067 [80]; 2004-832550 [82]; 2005-346574 [35]; 2005-591611 [60]
AB WO2004099134 A UPAB: 20060214
NOVELTY - Glutamine derivatives (I) are new.
DETAILED DESCRIPTION - Glutamine derivatives of formula NR1R2-C(=EWG1)-(CR3R4)n-CR5R6-CR7R8-CR9(NR10R11)-C(=EWG2)-PM (I) (excluding) are new.
n = 0 or 1;
R1-R11 = alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylheteroalkyl, heteroaryl-heteroalkyl, CHO, CO-R20, B(OH)2, CN, COOH, COOR21, CO-O-CO-R22, CO-NH(OH), CO-NR23(OH), CO-NH(OR24), CO-NH2, CO-NHR25, CO-NR26R27, HN-CO-R28, SO3H, SO2-NH2, SO2-NHR29, SO2-NR30R31, NH-SO2-R32, SO2-R33, OP(=O)(OH)2, OP(=O)(OR34)(OR35), P(=O)(OH)2, P(=O)(OR36)(OR37), halo, CF3, SH, S-R33, OH, O-R39, tetrazole, NH2, NHR40,

NR41R42 (all optionally at least mono substituted) or H;

R20-R42 = H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylheteroalkyl or heteroaryl-heteroalkyl;

EWG1, EWG2 = an electron withdrawing group;

PM = 1 of 15 specified groups given in the specification e.g. a group of formula (i);

X1 = CR51R52, O, S, SO, SO2 or NR53;

X2 = CR54R55, O, S, SO, SO2 or NR56;

R51-R56 = alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylheteroalkyl, heteroaryl-heteroalkyl, CHO, CO-R60, B(OH)2, CN, COOH, COOR61, CO-O-CO-R62, CO-NH(OH), CO-NR63(OH), CO-NH(OR64), CO-NH2, CO-NHR65, CO-NR66R67, HN-CO-R68, SO3H, SO2-NH2, SO2-NHR69, SO2-NR70R71, NH-SO2-R72, SO2-R73, OP(=O)(OH)2, OP(=O)(OR74)(OR75), P(=O)(OH)2, P(=O)(OR76)(OR77), halo, CF3, SH, S-R78, OH, O-R79, tetrazole, NH2, NHR80 or NR81R82 (all optionally at least mono substituted) or H, or

2 of R51-R56 = part of a ring;

R60-R82 = H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylheteroalkyl or heteroaryl-heteroalkyl, or

R66 + R67, R70 + R71 = part of a ring, or

R74 + R75, R76 + R77, R81 + R82 = part of a ring;

A1 = alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylheteroalkyl, heteroaryl-heteroalkyl, CHO, CO-R100, B(OH)2, CN, COOH, COOR101, CO-O-CO-R102, CO-NH(OH), CO-NR103(OH), CO-NH(OR104), CO-NH2, CO-NHR105, CO-NR106R107, HN-CO-R108, SO3H, SO2-NH2, SO2-NHR109, SO2-NR110R111, NH-SO2-R112, SO2-R113, OP(=O)(OH)2, OP(=O)(OR114)(OR115), P(=O)(OH)2, P(=O)(OR116)(OR117), halo, CF3, SH, S-R118, OH, O-R119, tetrazole, NH2, NHR120 or NR121R122 (all optionally at least mono substituted) or H;

R100-R122 = H, alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, cycloalkynyl, heteroalkyl, heteroalkenyl, heteroalkynyl, heterocycloalkyl, heterocycloalkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, arylheteroalkyl or heteroaryl-heteroalkyl, or

R106 + R107, R110 + R111 = part of a ring, or

R114 + R115, R116 + R117, R121 + R122 = part of a ring,

provided that glutamine-thiazolidine, glutamine-pyrrolidine, glutamine-pyrrolidine-2-carboxylic acid, glutaminepyrrolidine-2-carboxamide and (S,S)-4-amino-5-(2-cyano-2,5-dihydropyrrol-1-yl)-6-oxo-pentanoic acid amide, are excluded.

Full Definitions are given in the Definitions field (Full Definitions).

An INDEPENDENT CLAIM is included for a composition (C1) comprising (I) in combination with additional components e.g. acarbose and/or metformin.

ACTIVITY - Antidiabetic; Antilipemic; Vasotropic; Neuroprotective; Nephrotropic; Anorectic; Hypotensive; Cardiovascular-Gen.; Antiarteriosclerotic; Antiinflammatory; Antiulcer; Gastrointestinal-Gen.; Cytostatic; Osteopathic; Dermatological; Immunosuppressive; Antidepressant; Tranquilizer; Hypnotic; Muscular-Gen.; Immunomodulator; Neuroleptic; Anticonvulsant; Analgesic.

Tests are described, but no results are given.

MECHANISM OF ACTION - Dipeptidyl peptidase IV (DP IV) inhibitor.

USE - Used for treating non-insulin dependent diabetes mellitus (type 2), impaired glucose tolerance, impaired fasting glucose, impaired glucose metabolism, pre-diabetes, glucosuria, and disturbances of signal action at the cells of the islets of Langerhans and insulin sensitivity in the peripheral tissue in the post-prandial phase, insulin resistance, lipid

disorders, hyperlipidemia, metabolic acidosis, diabetic neuropathy and nephropathy and of sequelae caused by diabetes mellitus, obesity, metabolism-related hypertension and cardiovascular sequelae caused by hypertension, atherosclerosis and its sequelae, inflammatory bowel disease, including Crohn's disease and ulcerative colitis, other inflammatory conditions, pancreatitis, tumor metastasis, benign prostatic hypertrophy, gingivitis, osteoporosis, skin diseases and diseases of the mucosae, autoimmune diseases and inflammatory conditions, and psychosomatic, neuropsychiatric and depressive illness, and neurodegenerative diseases such as anxiety, depression, sleep disorders, chronic fatigue, schizophrenia, epilepsy, nutritional disorders, spasm, and chronic pain.

ADVANTAGE - (I) Have improved bioavailability resulting in a higher transport rate from the intestine into blood circulation, and exhibit decreased profile of side effects compared with ordinary dipeptidyl peptidase IV inhibitor.

Dwg.0/0

ACCESSION NUMBER: 2004-833676 [82] WPIDS
CROSS REFERENCE: 2004-805062 [79]; 2004-813067 [80]; 2004-832550 [82]; 2005-346574 [35]; 2005-591611 [60]
DOC. NO. CPI: C2004-289437
TITLE: New glutamine derivatives used for treating e.g. non-insulin dependent diabetes mellitus, obesity, atherosclerosis, inflammatory bowel disease and neurodegenerative diseases.
DERWENT CLASS: B05
INVENTOR(S): DEMUTH, H; HEISER, U; HOFFMANN, M; HOFFMANN, T; NIESTROJ, A; SCHILLING, S; NIESTROJ, A J
PATENT ASSIGNEE(S): (PROS-N) PROSIDION LTD
COUNTRY COUNT: 109
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2004099134	A2	20041118	(200482)*	EN	497
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NA NL OA PL PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BW BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NA NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
EP 1622870	A2	20060208	(200611)	EN	
R: AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LU MC NL PL PT RO SE SI SK TR					

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2004099134	A2	WO 2004-EP4774	20040505
EP 1622870	A2	EP 2004-731154	20040505
		WO 2004-EP4774	20040505

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1622870	A2 Based on	WO 2004099134

PRIORITY APPLN. INFO: US 2003-468014P 20030505; US 2003-467914P 20030505

L12 ANSWER 24 OF 59 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on

STN
TI Expression, purification, and C-terminal amidation of recombinant human glucagon-like peptide-1.
SO Protein Expression and Purification, (August 2004) Vol. 36, No. 2, pp. 292-299. print.
CODEN: PEXPEJ. ISSN: 1046-5928.
AU Zhang, Zhi-Zhen [Reprint Author]; Yang, Sheng-Sheng; Dou, Hong; Mao, Ji-Fang; Li, Kang-Sheng
AB Human glucagon-like peptide-1 (hGLP-1) (7-36) amide, a gastrointestinal hormone with a pharmaceutical potential in treating type 2 diabetes mellitus, is composed of 30 amino acid residues as a mature protein. We report here the development of a method for high-level expression and purification of recombinant hGLP-1 (7-36) amide (rhGLP-1) through glutathione S-transferase (GST) fusion expression system. The cDNA of hGLP-1-Leu, the 31st-residue leucine-extended precursor peptide, was prepared by annealing and ligating of artificially synthetic oligonucleotide fragments, inserted into pBluescript SK (+/-) plasmid, and then cloned into pGEX-4T-3 GST fusion vector. The fusion protein GST-hGLP-1-Leu, expressed in Escherichia coli strain BL21 (DE3), was purified by affinity chromatography after high-level culture and sonication of bacteria. Following cleavage of GST-hGLP-1-Leu by cyanogen bromide, the recombinant hGLP-1-Leu was released from fusion protein, and purified using QAE Sepharose ion exchange and RP C 18 chromatography. After purification, the precursor hGLP-1-Leu was transacylated by carboxypeptidase Y, Arg-NH2 as a nucleophile, to produce rhGLP-1. Electrospray ionization mass spectrometry showed the molecular weight was as expected. The biological activity of rhGLP-1 in a rat model demonstrated that plasma glucose concentrations were significantly lower and insulin concentrations higher after intraperitoneal injection of rhGLP-1 together with glucose compared with glucose alone ($P < 0.001$).

ACCESSION NUMBER: 2004:388928 BIOSIS
DOCUMENT NUMBER: PREV200400392012
TITLE: Expression, purification, and C-terminal amidation of recombinant human glucagon-like peptide-1.
AUTHOR(S): Zhang, Zhi-Zhen [Reprint Author]; Yang, Sheng-Sheng; Dou, Hong; Mao, Ji-Fang; Li, Kang-Sheng
CORPORATE SOURCE: Coll MedDept Microbiol and ImmunolJoint Influenza Res Ctr,SUMC and HKU, Shantou Univ, Shantou, Guangdong, 515041, China
zzz@stu.edu.cn
SOURCE: Protein Expression and Purification, (August 2004) Vol. 36, No. 2, pp. 292-299. print.
CODEN: PEXPEJ. ISSN: 1046-5928.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Oct 2004
Last Updated on STN: 6 Oct 2004

L12 ANSWER 25 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN DUPLICATE 4
TI OPTIMIZED PROMOTER CONSTRUCTS; COMPRISES NUCLEOTIDE SEQUENCES ASSOCIATED WITH EXPRESSION VECTORS FOR IMPROVING GENE TRANSFER AND EXPRESSION IN CELLS
INF Concino; Michael F., Bolton, MA, US
Heartlein; Michael W., Boxborough, MA, US
Kempinski; Heidi, Charlton, MA, US
Lamsa; Justin Chace, Westminster, MA, US
Selden; Richard F., Wellesley, MA, US
Treco; Douglas A., Arlington, MA, US
IN Concino Michael F; Heartlein Michael W; Kempinski Heidi; Lamsa Justin Chace; Selden Richard F; Treco Douglas A
AB The invention features constructs and related methods for expression of products in mammalian cells, e.g., human cells. Constructs include a

human gamma -actin, beta -actin, fibronectin, YY1, or beta -tubulin promoter region operably linked to a heterologous nucleic acid sequence.

CLMN 87 12 Figure(s).

FIGS. 1A-C shows the nucleotide sequence of a human gamma-actin promoter region from nucleotide-473 to nucleotide-7222 (SEQ ID NO: 1) of the promoter region. This sequence was identified by screening a human genomic leukocyte library using a probe derived from a known gamma-actin promoter region sequence (GenBank Accession No. M19283). FIG. 1D shows a diagram of the human gamma-actin promoter region

FIGS. 2A-D shows the nucleotide sequence of a human fibronectin promoter region (SEQ ID NO:2). This sequence was identified by screening a human genomic circulating whole blood library using a probe derived from known fibronectin promoter region sequence (GenBank Accession No. M26179 and/or M15801). FIG. 2E shows a diagram of the human fibronectin promoter region.

FIGS. 3A-E shows the nucleotide sequence of a human betatubulin promoter region (SEQ ID NO:3). This sequence was identified by screening a human genomic placental library using a probe derived from known beta-tubulin promoter region sequence (GenBank Accession No. X02344). FIG. 3F shows a diagram of the human beta-tubulin promoter region.

FIG. 4A shows the nucleotide sequence of a human YY1 promoter region (SEQ ID NO:4). This sequence was identified by screening a human genomic leukocyte library using a probe derived from known YY1 5' UTS region (GenBank Accession No. M77698, Z14077, and/or AF047455). FIG. 4B shows a diagram of the human YY1 promoter region.

FIG. 5A shows a plasmid map for a gamma-actin promoter regionbased construct, pXF8.941. The following elements are indicated on the construct. Human gamma-actin promoter; CMV enhancer at about cap-825, aldolase 5' UTS (including the intron from this region); the synthetic beta domain-deleted Factor VIII (hFVIII) cDNA; the 3' untranslated sequence from the hGH gene; sequences for plasmid replication in E. coli; and the amp gene for ampicillin selection in E. coli. FIG. 5B shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.941. Each point is the average (+-standard error) of hFVIII ELISA values determined for plasma samples taken from individual mice. Open circles are nude mice implanted with a hFVIII expressing human fibroblast clone transfected with pXF8.941. Closed circles are control animals injected with saline.

FIG. 6 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.971, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.

FIG. 7 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.914, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.

FIG. 8 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.973, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.

FIG. 9 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.751, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.

FIG. 10 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.753, which has

the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.

FIG. 11 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8. 1111, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.

FIG. 12 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.831, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice. Each line represents a different clone implanted into 5 nude mice.

AN	10480048 IFIPAT;IFIUDB;IFICDB
TITLE:	OPTIMIZED PROMOTER CONSTRUCTS; COMPRISES NUCLEOTIDE SEQUENCES ASSOCIATED WITH EXPRESSION VECTORS FOR IMPROVING GENE TRANSFER AND EXPRESSION IN CELLS
INVENTOR(S):	Concino; Michael F., Bolton, MA, US Heartlein; Michael W., Boxborough, MA, US Kempinski; Heidi, Charlton, MA, US Lamsa; Justin Chace, Westminster, MA, US Selden; Richard F., Wellesley, MA, US Treco; Douglas A., Arlington, MA, US
PATENT ASSIGNEE(S):	Unassigned
PATENT ASSIGNEE PROBABLE:	Transkaryotic Therapies Inc (Probable)
AGENT:	FISH & RICHARDSON PC, 225 FRANKLIN ST, BOSTON, MA, 02110, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003224477	A1	20031204
APPLICATION INFORMATION:	US 2002-160851		20020531
FAMILY INFORMATION:	US 2003224477		20031204

DOCUMENT TYPE:	Utility Patent Application - First Publication
FILE SEGMENT:	CHEMICAL APPLICATION
OTHER SOURCE:	CA 140:16608
NUMBER OF CLAIMS:	87 12 Figure(s).

DESCRIPTION OF FIGURES:

FIGS. 1A-C shows the nucleotide sequence of a human gamma-actin promoter region from nucleotide-473 to nucleotide-7222 (SEQ ID NO: 1) of the promoter region. This sequence was identified by screening a human genomic leukocyte library using a probe derived from a known gamma-actin promoter region sequence (GenBank Accession No. M19283). FIG. 1D shows a diagram of the human gamma-actin promoter region

FIGS. 2A-D shows the nucleotide sequence of a human fibronectin promoter region (SEQ ID NO:2). This sequence was identified by screening a human genomic circulating whole blood library using a probe derived from known fibronectin promoter region sequence (GenBank Accession No. M26179 and/or M15801). FIG. 2E shows a diagram of the human fibronectin promoter region.

FIGS. 3A-E shows the nucleotide sequence of a human betatubulin promoter region (SEQ ID NO:3). This sequence was identified by screening a human genomic placental library using a probe derived from known beta-tubulin promoter region sequence (GenBank Accession No. X02344). FIG. 3F shows a diagram of the human beta-tubulin promoter region.

FIG. 4A shows the nucleotide sequence of a human YY1 promoter region (SEQ ID NO:4). This sequence was identified by screening a human genomic leukocyte library using a probe derived from known YY1 5' UTS region (GenBank Accession No. M77698, Z14077, and/or AF047455). FIG. 4B shows a diagram of the human YY1 promoter region.

FIG. 5A shows a plasmid map for a gamma-actin promoter regionbased construct, pXF8.941. The following elements are indicated on the construct. Human gamma-actin promoter; CMV enhancer at about cap-825, aldolase 5' UTS (including the intron from this region); the synthetic beta domain-deleted Factor VIII (hFVIII) cDNA; the 3' untranslated sequence from the hGH gene; sequences for plasmid replication in E. coli; and the amp gene for ampicillin selection in E. coli. FIG. 5B shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.941. Each point is the average (+-standard error) of hFVIII ELISA values determined for plasma samples taken from individual mice. Open circles are nude mice implanted with a hFVIII expressing human fibroblast clone transfected with pXF8.941. Closed circles are control animals injected with saline.
FIG. 6 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.971, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.
FIG. 7 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.914, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.
FIG. 8 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.973, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.
FIG. 9 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.751, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.
FIG. 10 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.753, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.
FIG. 11 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8. 1111, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice at the times indicated on the X-axis. Each line represents a different clone implanted into 5 nude mice.
FIG. 12 shows in vivo expression of human Factor VIII in nude mice implanted with human fibroblasts transfected with pXF8.831, which has the regulatory elements indicated. Each point is the average of hFVIII ELISA values determined for plasma samples taken from individual mice. Each line represents a different clone implanted into 5 nude mice.

L12 ANSWER 26 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 5
TI New expression cassette comprising an operably linked nucleic acid sequence, useful for producing a tandem polypeptide that forms an inclusion body when expressed in a cell.
IN PENG, L; XIA, Y; HOLMQUIST, B; LUAN, P; WAGNER, F W
AN 2004-035129 [03] WPIDS
AB WO2003100022 A UPAB: 20040112
NOVELTY - An expression cassette (I), defined below in terms of its component parts, which produces a tandem polypeptide that forms an inclusion body when expressed in a cell, is new.
DETAILED DESCRIPTION - An expression cassette (I) which produces a tandem polypeptide that forms an inclusion body when expressed in a cell has the structure:
5' Pr-(TIS)D-(IBFP1)E-(CL1)G-ORF-(CL2-ORF)L -(CL3)M-(1BFP2)Q-(SSC)R-(CL4)T-(Ft)W-(Tr)X-3' (I), where
Pr = a promoter sequence;

TIS = encodes a translation initiation sequence;
IBFP1 = encodes a first inclusion body fusion partner comprising any of the 15 amino acid sequences or their variants;
CL1 = encodes a first cleavable peptide linker;
ORF = encodes a preselected polypeptide;
CL2 = encodes a second cleavable peptide linker;
CL3 = encodes a third cleavable peptide linker;
IBFP2 = encodes a second inclusion body fusion partner;
SSC = a suppressable stop codon;
CL4 = encodes a fourth cleavable peptide linker;
Ft = encodes a fusion tag;
Tr = a transcription terminator sequence;
D or X = independently 0 or an integer of 1-4;
R = 0 or an integer of 1-2; and
E, G, L, M, Q, T or W = independently 0 or an integer of 1-20.
INDEPENDENT CLAIMS are also included for the following:
(1) an RNA produced by transcription of the expression cassette;
(2) a tandem polypeptide produced by translation of the RNA;
(3) a nucleic acid construct comprising a vector and the expression cassette;
(4) a cell comprising the nucleic acid construct;
(5) a DNA sequence that encodes the tandem polypeptide; and
(6) selecting an amino acid sequence of an inclusion body fusion partner that confers isolation enhancement to an inclusion body, and producing a tandem polypeptide.
USE - The expression cassette is useful for producing peptide and polypeptide in a cell, preferably a tandem polypeptide that forms an inclusion body when expressed in a cell (claimed).
Dwg.0/13

ACCESSION NUMBER: 2004-035129 [03] WPIDS
DOC. NO. CPI: C2004-011670
TITLE: New expression cassette comprising an operably linked nucleic acid sequence, useful for producing a tandem polypeptide that forms an inclusion body when expressed in a cell.
DERWENT CLASS: B04 D16
INVENTOR(S): PENG, L; XIA, Y; HOLMQUIST, B; LUAN, P; WAGNER, F W
PATENT ASSIGNEE(S): (REST-N) RESTORAGEN INC; (HOLM-I) HOLMQUIST B; (LUAN-I) LUAN P; (WAGN-I) WAGNER F W; (XIAY-I) XIA Y
COUNTRY COUNT: 104
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003100022	A2	20031204	(200403)*	EN	132
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003231862	A1	20031212	(200443)		
EP 1554302	A2	20050720	(200547)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
US 2005239172	A1	20051027	(200571)		
AU 2003231862	A8	20051103	(200629)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003100022	A2	WO 2003-US16645	20030523

AU 2003231862	A1		AU 2003-231862	20030523
EP 1554302	A2		EP 2003-755504	20030523
			WO 2003-US16645	20030523
US 2005239172	A1	Provisional	US 2002-383212P	20020524
		Cont of	WO 2003-US16645	20030523
			US 2004-997700	20041124
AU 2003231862	A8		AU 2003-231862	20030523

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003231862	A1	Based on	WO 2003100022
EP 1554302	A2	Based on	WO 2003100022
AU 2003231862	A8	Based on	WO 2003100022

PRIORITY APPLN. INFO: US 2002-383212P 20020524; US 2004-997700 20041124

L12 ANSWER 27 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN DUPLICATE 6
TI New expression cassette comprising an operably linked nucleic acid sequence, useful for producing a tandem polypeptide that forms an inclusion body when expressed in a cell.
IN HARLEY, S; LUAN, P; WILLIAMS, J A; XIA, Y
AN 2004-035128 [03] WPIDS
AB WO2003100021 A UPAB: 20040112
NOVELTY - An expression cassette comprising the operably linked nucleic acid sequence of (I), where the expression of the cassette produces a tandem polypeptide that forms an inclusion body when expressed in a cell, is new.

DETAILED DESCRIPTION - An expression cassette comprising the operably linked nucleic acid sequence of (I), where the expression of the cassette produces a tandem polypeptide that forms an inclusion body when expressed in a cell, is new.

(I) 5' Pr-(TIS)D-(IBFP1)E-(CL1)G-ORF-(CL2-ORF)L -(CL3)M-(1BFP2)Q-(SSC)R-(CL4)T-(Ft)W-(Tr)X-3',

Pr = a promoter sequence;

TIS = encodes a translation initiation sequence;

IBFP1 = encodes a first inclusion body fusion partner comprising any of the 15 amino acid sequences or their variants;

CL1 = encodes a first cleavable peptide linker;

ORF = encodes a preselected polypeptide;

CL2 = encodes a second cleavable peptide linker;

CL3 = encodes a third cleavable peptide linker;

IBFP2 = encodes a second inclusion body fusion partner;

SSC = a suppressable stop codon;

CL4 = encodes a fourth cleavable peptide linker;

Ft = encodes a fusion tag;

Tr = a transcription terminator sequence;

D or X = independently 0 or an integer of 1-4;

R is 0 or an integer of 1-2; and E, G, L, M, Q, T or W is independently 0 or an integer of 1-20

INDEPENDENT CLAIMS are also included for:

(1) an RNA produced by transcription of the expression cassette;

(2) a tandem polypeptide produced by translation of the RNA;

(3) a nucleic acid construct comprising a vector and the expression cassette;

(4) a cell comprising the nucleic acid construct;

(5) a DNA sequence that encodes the tandem polypeptide;

(6) selecting an amino acid sequence of an inclusion body fusion partner that confers isolation enhancement to an inclusion body; and

(7) producing a tandem polypeptide.

USE - The expression cassette is useful for producing peptide and polypeptide in a cell, preferably a tandem polypeptide that forms an

inclusion body when expressed in a cell (claimed).
Dwg.0/19

ACCESSION NUMBER: 2004-035128 [03] WPIDS
DOC. NO. CPI: C2004-011669
TITLE: New expression cassette comprising an operably linked nucleic acid sequence, useful for producing a tandem polypeptide that forms an inclusion body when expressed in a cell.
DERWENT CLASS: B04 D16
INVENTOR(S): HARLEY, S; LUAN, P; WILLIAMS, J A; XIA, Y
PATENT ASSIGNEE(S): (HARL-I) HARLEY S; (REST-N) RESTORAGEN INC; (LUAN-I) LUAN P; (WILL-I) WILLIAMS J A; (XIAY-I) XIA Y
COUNTRY COUNT: 104
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003100021	A2	20031204	(200403)*	EN	157
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003239895	A1	20031212	(200443)		
EP 1532261	A2	20050525	(200535)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
US 2005221444	A1	20051006	(200566)		
JP 2006508639	W	20060316	(200620)		115

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2003100021	A2		WO 2003-US16643	20030523
AU 2003239895	A1		AU 2003-239895	20030523
EP 1532261	A2		EP 2003-734201	20030523
			WO 2003-US16643	20030523
US 2005221444	A1	Provisional	US 2002-383370P	20020524
		Cont of	WO 2003-US16643	20030523
			US 2004-997078	20041124
JP 2006508639	W		WO 2003-US16643	20030523
			JP 2004-508263	20030523

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003239895	A1	Based on	WO 2003100021
EP 1532261	A2	Based on	WO 2003100021
JP 2006508639	W	Based on	WO 2003100021

PRIORITY APPLN. INFO: US 2002-383370P 20020524; US 2004-997078 20041124

L12 ANSWER 28 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI GLP-1 GENE DELIVERY FOR THE TREATMENT OF TYPE 2 DIABETES; PLASMID COMPRISING A CHICKEN BETA ACTIN PROMOTER AND ENHANCER; A MODIFIED GLP-1 (7-37) CDNA (P BETA GLP1), CARRYING A FURIN CLEAVAGE SITE
INF Ko; Kyungsoo, Seoul, KR
Lee; Minhyung, Seoul, KR
Oh; Seungjoon, Seoul, KR

IN Ko Kyungsoo (KR); Lee Minhyung (KR); Oh Seungjoon (KR)
AB This patent discloses compositions and methods of use thereof to normalize the blood glucose levels of patients with type 2 diabetes. It relates particularly to a plasmid comprising a chicken beta actin promoter and enhancer; a modified GLP-1 (737) cDNA (p beta GLP1), carrying a furin cleavage site, which is constructed and delivered into a cell for the expression of active GLP-1.
CLMN 19 4 Figure(s).
FIG. 1 is a schematic representation of plasmid p beta GLP1 carrying a modified GLP-1 (7-37) cDNA sequence and a furin cleavage site.
FIG. 2 shows the RT-PCR assay of the production of GLP-1 in HepG2 cells transfected by the transfection composition containing p beta GLP1/gene carrier complexes.
FIG. 3 shows the insulin secretion of co-cultured islets with HepG2 cells transfected by the transfection composition containing p beta GLP1/gene carrier complexes.
FIG. 4. illustrates the therapeutic effect of the transfection composition containing p beta GLP1/PAGA complexes in Zucker Diabetic Fatty(ZDF) rats.

AN	10475845 IFIPAT;IFIUDB;IFICDB
TITLE:	GLP-1 GENE DELIVERY FOR THE TREATMENT OF TYPE 2 DIABETES; PLASMID COMPRISING A CHICKEN BETA ACTIN PROMOTER AND ENHANCER; A MODIFIED GLP-1 (7-37) CDNA (P BETA GLP1), CARRYING A FURIN CLEAVAGE SITE
INVENTOR(S):	Ko; Kyungsoo, Seoul, KR Lee; Minhyung, Seoul, KR Oh; Seungjoon, Seoul, KR
PATENT ASSIGNEE(S):	Expression Genetics, Inc.
AGENT:	THORPE NORTH WESTERN, 8180 SOUTH 700 EAST, SUITE 200, P.O. BOX 1219, SANDY, UT, 84070, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003220274	A1	20031127
APPLICATION INFORMATION:	US 2002-153470		20020521
FAMILY INFORMATION:	US 2003220274		20031127
DOCUMENT TYPE:	Utility Patent Application - First Publication		
FILE SEGMENT:	CHEMICAL APPLICATION		
OTHER SOURCE:	CA 140:1541		

NUMBER OF CLAIMS: 19 4 Figure(s).
DESCRIPTION OF FIGURES:
FIG. 1 is a schematic representation of plasmid p beta GLP1 carrying a modified GLP-1 (7-37) cDNA sequence and a furin cleavage site.
FIG. 2 shows the RT-PCR assay of the production of GLP-1 in HepG2 cells transfected by the transfection composition containing p beta GLP1/gene carrier complexes.
FIG. 3 shows the insulin secretion of co-cultured islets with HepG2 cells transfected by the transfection composition containing p beta GLP1/gene carrier complexes.
FIG. 4. illustrates the therapeutic effect of the transfection composition containing p beta GLP1/PAGA complexes in Zucker Diabetic Fatty(ZDF) rats.

L12 ANSWER 29 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI GLUCOSE-DEPENDENT INSULIN-SECRETING CELLS TRANSFECTED WITH A NUCLEOTIDE SEQUENCE ENCODING GLP-1; INSULIN-SECRETING CELL WHICH CODES AND EXPRESSES GLUCAGON-LIKE PEPTIDES-1 (GLP-1) FOR TREATING DIABETES AND AUTOIMMUNE DISEASES
INF Hui; Hongxiang, Los Angeles, CA, US
Perfetti; Riccardo, Los Angeles, CA, US
IN Hui Hongxiang; Perfetti Riccardo
AB Disclosed herein are cells that secrete insulin in a glucosedependent manner. The cell line comprises insulin-secreting cells that have been

transfected with a minigene construct comprising a nucleotide sequence encoding for glucagon-like peptide-1 (GLP-1). In preferred embodiments, the minigene construct is operatively associated with a promoter. The cell line may be used to treat diabetes or other conditions in which delivering insulin in a glucose-dependent manner would be advantageous, to investigate the function and development of pancreatic cells, and to test the efficacy of drugs that stimulate insulin secretion. The cells may be implanted in a mammal, or may be included in a device that resides exterior to the mammal, yet which delivers insulin to the mammal in response to the glucose level of a body fluid in contact therewith. The minigene construct may also be implemented in conjunction with an in vivo gene transfer approach.

CLMN 46 10 Figure(s).

FIGS. 1A-C are schematic representations of plasmid constructs. FIGS. 1A and 1B are representations of two plasmid constructs (A: CMV/GLP-1 and B: RIP/GLP-1) generated with a human GLP-1 minigene. FIG. 1C is a representation of an area of a human proglucagon gene utilized to generate a GLP-1 insert.

FIGS. 2A-B depict a northern blot analysis of control and GLP-1transfected MIN-6 cells, respectively. Parental MIN-6 cells, MIN-6 cells transfected with the vector alone, or with a vector containing a DNA sequence encoding for human GLP-1 were cultured in 10% FBS, in the presence of 12 mM glucose. Cells were subjected to RNA extraction and northern blot analysis for GLP-1, insulin, and beta-actin mRNA levels. FIG. 2A depicts cells transfected with a plasmid containing human GLP-1 driven by the CMV promoter (Lane 1); parental MIN-6 cells (Lane 2); and MIN-6 cells transfected with the vector alone (Lane 3). FIG. 2B depicts cells transfected with a plasmid containing human GLP-1 driven by the rat insulin promoter (Lane 4), and parental MIN-6 cells (Lane 5). Each experiment was repeated twice, using RNA samples from independent cultures.

FIGS. 3A-F depict northern blot analysis for insulin and GLP-1 mRNAs. Cells routinely cultured in the presence of 10% FBS and 12 mM glucose were subjected to a 2-hour wash out period with medium deprived of glucose and FBS. They were then cultured in serum-free medium for 8 hours in the presence of various concentrations of glucose (e.g., 0 mM, 0.1 mM, 1 mM, 3 mM, 6 mM, 10 mM, and 20 mM). After RNA extraction, the membranes were hybridized with cDNA probes for insulin, GLP-1 and beta-actin. FIGS. 3A-C represent one individual experiment, while FIGS. 3DF are the graphical average of at least three independent northern blot analyses. FIGS. 3A and 3D: parental MIN-6 cells; Panels 3B and 3E: MIN-6 CMV/GLP-1 cells; and FIGS. 3C and 3F: MIN-6 RIP/GLP-1 cells. Insulin and GLP-1 mRNA levels were normalized by beta-actin mRNA levels for each individual blot. Statistical significance of the data was evaluated by ANOVA.

FIG. 4 graphically depicts a glucose-dependent insulin secretion in a culture medium. Insulin accumulation into the culture medium was determined after a 2-hour wash out period, carried out with serum-free and glucose-free medium. Parental MIN-6 cells, MIN-6 cells transfected with the vector alone, MIN-6 cells transfected with CMV/GLP-1, and MIN-6 cells transfected with RIP/GLP-1 were incubated in the presence of various concentrations of glucose for 8 hours. Each experiment was repeated at least four times and the data plotted on the graph represent the mean plus or minus one standard deviation. Insulin levels were normalized by the total protein level in each individual culture. Statistical significance of the data was evaluated by ANOVA.

FIG. 5 graphically depicts inhibition of insulin secretion by the GLP-1 receptor antagonist Exendin-9. MIN-6 RIP/GLP-1 cells routinely cultured in the presence of 10% FBS and 12 mM glucose were subjected to an overnight wash out period

with medium deprived of glucose and FBS. They were then cultured in serumfree medium in the presence of 10 mM glucose and Exendin-9 (106 M) for increasing lengths of time. Insulin levels were normalized for protein content. Statistical significance of the data was evaluated by unpaired Student's t test.

FIG. 6 graphically depicts glucose-dependent GLP-1 secretion in a culture medium. GLP-1 accumulation into the culture medium was determined after a 2-hour wash out period, carried out with serum-free and glucose-free medium. Parental MIN-6 cells, MIN-6 cells transfected with the vector alone, MIN-6 cells transfected with CMV/GLP-1, and MIN-6 cells transfected with RIP/GLP-1 were incubated in the presence of various concentrations of glucose for 8 hours. Each experiment was repeated at least four times and the data plotted on the graph represent the mean plus or minus one standard deviation. GLP-1 levels were normalized by the total protein level in each individual culture. Statistical significance of the data was evaluated by ANOVA.

FIG. 7 is executed in color, and depicts the immunofluorocytochemistry for IDX-1 in cells exposed to various concentrations of glucose. CMV/ GLP-1 cells, RIP/GLP-1 cells, as well as parental MIN-6 cells, were cultured in the presence of 6 mM glucose with 10% FBS. After a 2-hour wash-out incubation with glucose-free, serum-free medium, they were incubated with 0 mM, 6 mM or 12 mM glucose for 12 hours and subjected to immunostaining with an anti-IDX-1 antibody. FIGS. 7A, 7B, and 7C represent parental MIN-6 cells cultured in glucose-free medium (A), 6 mM glucose (B), and 12 mM glucose (C), respectively. FIGS. 7D, 7E, and 7F represent CMV/GLP-1 MIN-6 cells cultured in glucose-free medium (D), 6 mM glucose (E), and 12 mM glucose (F), respectively. FIGS. 7G, 7H and 71 represent RIP/GLP-1 MIN-6 cells cultured in glucose-free medium (G), 6 mM glucose (H), and 12 mM glucose (I), respectively.

FIGS. 8A-B depict GLP-1 receptor expression in MIN-6 cells transfected with RIP/GLP-1. MIN-6 cells transfected with RIP/ GLP-1 were cultured in serum-free medium in the presence of various concentrations of glucose (e.g., 0 mM, 3 mM, 6 mM, and 15 mM) for 48 hours. After removal of the culture medium, the cells were collected and the protein extract subjected to western blot analysis with a polyclonal antibody directed against human GLP-1 receptor. FIG. 8A depicts an individual western blot analysis, and FIG. 8B graphically depicts the average of three independent experiments, with the GLP-1 receptor levels normalized by the total protein content of each individual cell extract.

FIGS. 9A-B depict glucose- and GLP-1-dependent binding of IDX-1 to the rat insulin promoter A1 element. Nuclear extract from RIP/GLP-1 MIN-6 cells cultured in the presence of different concentrations of glucose were analyzed by electrophoretic mobility shift assays (EMSA) for binding to the A1 element of the insulin promoter gamma 32P-labeled probe. FIG. 9A: Lane 1 indicates incubation of the radiolabeled A1 oligonucleotide sequence in the absence of nuclear extracts; Lane 2 indicates nuclear extracts incubated in the presence of a 100 x nonlabeled A1 oligonucleotide sequence, and a labeled element (cells were cultured in the presence of 10 mM glucose); Lane 3 through Lane 7 indicate nuclear extracts of cells cultured in the presence of 0 mM, 3 mM, 6 mM, 10 mM and 15 mM glucose, respectively; Lane 8 indicates incubation of nuclear extracts of cells cultured with 15 mM glucose in the presence of an IDX1 antibody. FIG. 9B depicts the binding of nuclear proteins to the A1 element of the insulin promoter from RIP/GLP -1 MINE cells cultured in the presence of different concentrations of glucose. The bar graph represents the average of three independent experiments and is expressed in arbitrary units with the binding to cells cultured in the absence of glucose considered equal to 1. Statistical significance of the data was evaluated by

Student's t test.

FIGS. 10A-C depict an effect of cAMP inhibition on glucose and GLP -1-dependent secretion of insulin and insulin mRNA levels. MIN-6 RIP/GLP-1 cells routinely cultured in the presence of 10% FBS and 12 mM glucose were subjected to an overnight wash out period with medium deprived of glucose and FBS. They were then cultured in serum-free medium in the presence of 10 mM glucose in the presence of Rp-cAMP (10-6 M). FIG. 10A depicts cAMP levels normalized for protein content. FIG. 10B depicts the amount of insulin released into the culture medium. FIG. 10C depicts mRNA levels for insulin and p-actin. The blot in FIG. 10C indicates one individual experiment. Repetition of the experiment using RNA extracts from independent cultures produced very similar results. Statistical significance of the data for mRNA and protein levels were evaluated by unpaired Student's t test.

AN	10442010 IFIPAT;IFIUDB;IFICDB
TITLE:	GLUCOSE-DEPENDENT INSULIN-SECRETING CELLS TRANSFECTED WITH A NUCLEOTIDE SEQUENCE ENCODING GLP-1; INSULIN-SECRETING CELL WHICH CODES AND EXPRESSES GLUCAGON-LIKE PEPTIDES-1 (GLP-1) FOR TREATING DIABETES AND AUTOIMMUNE DISEASES
INVENTOR(S):	Hui; Hongxiang, Los Angeles, CA, US Perfetti; Riccardo, Los Angeles, CA, US
PATENT ASSIGNEE(S):	Unassigned
PATENT ASSIGNEE PROBABLE:	Cedars-Sinai Medical Center (Probable)
AGENT:	Richard H. Zaitlen, Esq. PILLSBURY WINTHROP LLP, Suite 2800, 725 South Figueroa Street, Los Angeles, CA, 90017-5406, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003186436	A1	20031002
APPLICATION INFORMATION:	US 2002-97230		20020312
FAMILY INFORMATION:	US 2003186436		20031002

DOCUMENT TYPE:	Utility Patent Application - First Publication
FILE SEGMENT:	CHEMICAL APPLICATION
NUMBER OF CLAIMS:	46 10 Figure(s).

DESCRIPTION OF FIGURES:

FIGS. 1A-C are schematic representations of plasmid constructs. FIGS. 1A and 1B are representations of two plasmid constructs (A: CMV/ ***GLP*** -1 and B: RIP/GLP-1) generated with a human GLP-1 minigene. FIG. 1C is a representation of an area of a human proglucagon gene utilized to generate a GLP-1 insert.

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FIGS. 3A-F depict northern blot analysis for insulin and GLP- ***1*** mRNAs. Cells routinely cultured in the presence of 10% FBS and 12 mM glucose were subjected to a 2-hour wash out period with medium deprived of glucose and FBS. They were then cultured in serum-free medium for 8 hours in the presence of various concentrations of glucose (e.g., 0 mM, 0.1 mM, 1 mM, 3

mM, 6 mM, 10 mM, and 20 mM). After RNA extraction, the membranes were hybridized with cDNA probes for insulin, GLP-1 and beta-actin. FIGS. 3A-C represent one individual experiment, while FIGS. 3DF are the graphical average of at least three independent northern blot analyses. FIGS. 3A and 3D: parental MIN-6 cells; Panels 3B and 3E: MIN-6 CMV/GLP -1 cells; and FIGS. 3C and 3F: MIN-6 RIP/GLP-1 cells. Insulin and GLP-1 mRNA levels were normalized by beta-actin mRNA levels for each individual blot. Statistical significance of the data was evaluated by ANOVA.

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FIG. 5 graphically depicts inhibition of insulin secretion by the GLP -1 receptor antagonist Exendin-9. MIN-6 RIP/GLP- ***1*** cells routinely cultured in the presence of 10% FBS and 12 mM glucose were subjected to an overnight wash out period with medium deprived of glucose and FBS. They were then cultured in serumfree medium in the presence of 10 mM glucose and Exendin-9 (106 M) for increasing lengths of time. Insulin levels were normalized for protein content. Statistical significance of the data was evaluated by unpaired Student's t test.

FIG. 6 graphically depicts glucose-dependent GLP-1 secretion in a culture medium. GLP-1 accumulation into the culture medium was determined after a 2-hour wash out period, carried out with serum-free and glucose-free medium. Parental MIN-6 cells, MIN-6 cells transfected with the vector alone, MIN-6 cells transfected with CMV/ ***GLP*** -1, and MIN-6 cells transfected with RIP/GLP- ***1*** were incubated in the presence of various concentrations of glucose for 8 hours. Each experiment was repeated at least four times and the data plotted on the graph represent the mean plus or minus one standard deviation. GLP-1 levels were normalized by the total protein level in each individual culture. Statistical significance of the data was evaluated by ANOVA.

FIG. 7 is executed in color, and depicts the immunofluorocytochemistry for IDX-1 in cells exposed to various concentrations of glucose. CMV/GLP- ***1*** cells, RIP/GLP-1 cells, as well as parental MIN-6 cells, were cultured in the presence of 6 mM glucose with 10% FBS. After a 2-hour wash-out incubation with glucose-free, serum-free medium, they were incubated with 0 mM, 6 mM or 12 mM glucose for 12 hours and subjected to immunostaining with an anti-IDX-1 antibody. FIGS. 7A, 7B, and 7C represent parental MIN-6 cells cultured in glucose-free medium (A), 6 mM glucose (B), and 12 mM glucose (C), respectively. FIGS. 7D, 7E, and 7F represent CMV/GLP -1 MIN-6 cells cultured in glucose-free medium (D), 6 mM glucose (E), and 12 mM glucose (F), respectively. FIGS. 7G, 7H and 71 represent RIP/ ***GLP*** -1 MIN-6 cells cultured in glucose-free medium (G), 6 mM glucose (H), and 12 mM glucose (I), respectively.

FIGS. 8A-B depict GLP-1 receptor expression in MIN-6 cells transfected with RIP/GLP-1. MIN-6 cells transfected with RIP/ GLP-1 were cultured in serum-free medium in the presence of various concentrations of glucose (e.g., 0 mM, 3 mM, 6 mM, and 15 mM) for 48 hours. After removal of the culture medium, the cells were collected and the protein extract subjected to western blot analysis with a polyclonal antibody directed against human GLP-1 receptor. FIG. 8A depicts an individual western blot analysis, and FIG. 8B graphically depicts the average of three independent experiments, with the ***GLP*** -1 receptor levels normalized by the total protein content of each individual cell extract.

FIGS. 9A-B depict glucose- and GLP-1-dependent binding of IDX-1 to the rat insulin promoter A1 element. Nuclear extract from RIP/***GLP*** -1 MIN-6 cells cultured in the presence of different concentrations of glucose were analyzed by electrophoretic mobility shift assays (EMSA) for binding to the A1 element of the insulin promoter gamma 32P-labeled probe. FIG. 9A: Lane 1 indicates incubation of the radiolabeled A1 oligonucleotide sequence in the absence of nuclear extracts; Lane 2 indicates nuclear extracts incubated in the presence of a 100 x nonlabeled A1 oligonucleotide sequence, and a labeled element (cells were cultured in the presence of 10 mM glucose); Lane 3 through Lane 7 indicate nuclear extracts of cells cultured in the presence of 0 mM, 3 mM, 6 mM, 10 mM and 15 mM glucose, respectively; Lane 8 indicates incubation of nuclear extracts of cells cultured with 15 mM glucose in the presence of an IDX1 antibody. FIG. 9B depicts the binding of nuclear proteins to the A1 element of the insulin promoter from RIP/***GLP*** -1 MINE cells cultured in the presence of different concentrations of glucose. The bar graph represents the average of three independent experiments and is expressed in arbitrary units with the binding to cells cultured in the absence of glucose considered equal to 1. Statistical significance of the data was evaluated by Student's t test. FIGS. 10A-C depict an effect of cAMP inhibition on glucose and GLP-***1*** -dependent secretion of insulin and insulin mRNA levels. MIN-6 RIP/***GLP*** -1 cells routinely cultured in the presence of 10% FBS and 12 mM glucose were subjected to an overnight wash out period with medium deprived of glucose and FBS. They were then cultured in serum-free medium in the presence of 10 mM glucose in the presence of Rp-cAMP (10-6 M). FIG. 10A depicts cAMP levels normalized for protein content. FIG. 10B depicts the amount of insulin released into the culture medium. FIG. 10C depicts mRNA levels for insulin and p-actin. The blot in FIG. 10C indicates one individual experiment. Repetition of the experiment using RNA extracts from independent cultures ***produced*** very similar results. Statistical significance of the data for mRNA and protein levels were evaluated by unpaired Student's t test.

L12 ANSWER 30 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI COLLECTIONS OF TRANSGENIC ANIMAL LINES (LIVING LIBRARY); TRANSGENIC ANIMAL FOR USE AS TOOLS IN GENOMICS
INF Serafini; Tito Andrew, San Mateo, CA, US
IN Serafini Tito Andrew
AB The invention provides collections of transgenic animals and vectors for producing transgenic animals, which transgenic animals and vectors have a transgene comprising sequences encoding a detectable or selectable marker, the expression of which marker is under the control of regulatory sequences from an endogenous gene such that when the transgene is present in the genome of the transgenic animal, the detectable or selectable marker has the same expression pattern as the endogenous gene. Such transgenic animals can then be used to detect, isolate and/or select pure populations of cells having a particular functional characteristic. The isolated cells have uses in gene discovery, target identification and validation, genomic and proteomic analysis, etc.
CLMN 158

AN	10306855 IFIPAT;IFIUDB;IFICDB		
TITLE:	COLLECTIONS OF TRANSGENIC ANIMAL LINES (LIVING LIBRARY); TRANSGENIC ANIMAL FOR USE AS TOOLS IN GENOMICS		
INVENTOR(S):	Serafini; Tito Andrew, San Mateo, CA, US		
PATENT ASSIGNEE(S):	Unassigned		
PATENT ASSIGNEE PROBABLE:	Renovis Inc (Probable)		
AGENT:	PENNIE AND EDMONDS, 1155 AVENUE OF THE AMERICAS, NEW YORK, NY, 100362711		
	NUMBER	PK	DATE
PATENT INFORMATION:	US 2003051266	A1	20030313
APPLICATION INFORMATION:	US 2001-783487		20010214

FAMILY INFORMATION: US 2003051266 20030313
DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 158

L12 ANSWER 31 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI Endocrine cell lines originated from mammalian hypothalamus and pancreatic islet, applicable in expression cloning systems of bioactive peptide precursor genes, and in screening G protein-coupled receptor ligands.
IN KISHIMOTO, K; KUNITOMO, H; MIURA, K; NISHI, T; OBINATA, M; SAEKI, S; SASAKI, K; YOSHIZAWA, M
AN 2003-833737 [77] WPIDS
AB WO2003087366 A UPAB: 20031128
NOVELTY - Obtaining a DNA that encodes a peptide acting as agonist, antagonist or inverse agonist on a target receptor comprises transformation of endocrine cell-originated cell lines after transferring arbitrary cDNAs or chromosomal DNAs; culturing the transformants and contacting with cells expressing the target receptor; and detecting the response reaction for identification, is new.

DETAILED DESCRIPTION - A method for obtaining a DNA that encodes a peptide acting as agonist, antagonist or inverse agonist on a target receptor comprises:

(a) transformation of endocrine cell-originated cell lines after transferring arbitrary cDNAs or chromosomal DNAs;

(b) culturing the transformants to express the transferred DNAs before contacting the culture supernatant, cell extract, membrane fraction or transformant cell lines themselves with the target receptor-expressing cells;

(c) detecting the response reaction of such cells based on the receptor;

(d) selecting a transformant cell line with the target activity as indication; and

(e) identification of the DNA that can provide such target activity in the DNA-transferred transformant cell line.

INDEPENDENT CLAIMS are also included for:

(1) obtaining a DNA that encodes a peptide acting as agonist, antagonist or inverse agonist on a target receptor comprising;

(a) production of expression vectors from a cDNA library with pools of 1-10,000 clones;

(b) transformation of endocrine cell-originated cell lines by transferring a mixture of cDNA lines from the pools;

(c) culturing the transformants to express the transferred DNAs before contacting the culture supernatant, cell extract, membrane fraction or transformant cell lines themselves with the target receptor-expressing cells;

(d) detecting the response reaction of such cells based on the receptor;

(e) selecting a pool that encodes the target activity;

(f) repeating the procedures (b)-(e) on the pool-containing 1 clone; and

(g) identifying the cDNA that can provide the target activity in the transformant cell line;

(2) cell lines originated from hypothalamus or pancreatic islet expressing 1 or more endogenous genes of leptin receptor (Ob-Rb) gene, prepro-neuromedein U gene, RFamide-related eptide (RFRP) prepro-protein gene, prepro-olexin gene, cocaine and amphetamine-regulated transcript (CART) gene, NMU2R gene, RFRP receptor gene, MC4R gene, NPY1R gene, NPFF2 gene, CRHR-1 gene, CRHR-2 gene, MCHR1 gene, CNTF receptor gene, NMU1R gene, OX1R gene, OX2R gene, GLP-1 receptor gene, GLP-2 receptor gene, prepro-insulin gene, PC1 gene, PC2 gene, PDX1 gene, Pax4 gene, Pax6 gene and Nkx2.2 gene (32 and 28 genes from cells in

hypothalamus and pancreatic islet, respectively, as specified); or these peptides expressed by them;

(3) immortalized cell lines obtained from the specific gene-expressing hypothalamus or Langerhan's islet in the non-human transgenic animals transferred with the large T antigen gene of an SV40 temperature-sensitive mutant strain;

(4) a process for producing these peptides by culturing the cell lines before isolation;

(5) detecting or obtained peptides acting as agonists, antagonists or inverse agonists on a target receptor by using the already-specified method with the cell lines for identification;

(6) cell lines originated from serum-free acclimatized B cell line for expression of EBNA-1 gene of Epstein-Barr virus after integrating the chromosomal DNA with:

(a) a DNA construct for expressing the necessary transcription factor in the construction of an induction expression system;

(b) a DNA construct obtained by ligating a reporter gene to downstream of a promoter containing a transcription factor-responsive sequence; or/and

(c) a DNA construct for expressing Galpha protein or chimeric Galpha protein;

(7) obtaining a DNA that encodes the peptide, particularly receptor, that reacts with a test substance by using the cell lines in (6) for carrying out the already-specified methods;

(8) structurally-active mutant G protein-coupled receptors (GCPRs) thus obtained;

(9) screening or obtaining MC1R antagonists by using type 1 melanocortin receptor (MC1R) and proadrenomedullin N-20 terminal peptide (PAMP) or a peptide containing amino acid residues 9-20 from the N-terminal of PAMP;

(10) screening or obtaining GPR43 or GPR41 antagonists by using orphan G protein-coupled receptor GPR43 or GPR41, respectively, and acetic acid, propionic acid, acetate or propionate;

(11) screening or obtaining G10d antagonists by using orphan G protein-coupled receptor G10d and alpha-melanocyte-stimulating hormone or adrenocorticotrophin-stimulating hormone;

(12) obtaining G protein-coupled receptor agonists comprising:

(a) transformation of any of the cell lines with a transferred DNA that encodes an arbitrary G protein-coupled receptor;

(b) expressing the DNA for contact with a test substance; and

(c) assaying the response reaction and comparing with a control;

(13) obtaining antagonists of a G protein-coupled receptor comprising:

(a) transformation of any of the cell lines with a transferred DNA that encodes an arbitrary G protein-coupled receptor;

(b) expressing the DNA for contact with an agonist of the receptor in the presence of a test substance;

(c) assaying the response reaction; and

(d) selecting the test substance that can eliminate the response reaction of the agonist-based transformant;

(14) obtaining inverse agonists of a G protein-coupled receptor by using the reporter gene-incorporated transformant cell lines with measurement of expression of the reporter gene for indication;

(15) obtaining activators or inhibitors of a peptide such as transcription factor, signal-transducing molecule or enzyme by using the specified peptide gene-transferred cell lines; and

(16) host-vector systems based on the cell lines with arbitrary promoters and an expression vector containing the oriP of Epstein-Barr virus as vector.

USE - The cell lines are applicable in expression cloning systems of bioactive peptide precursor genes, and in screening GCPR ligands for use in drugs, including agonists, antagonists and inverse agonists like activators and inhibitors (all claimed).

ADVANTAGE - Such cell lines can provide a highly sensitive and convenient GPCR ligand assay system.
Dwg.0/17

ACCESSION NUMBER: 2003-833737 [77] WPIDS
DOC. NO. CPI: C2003-234648
TITLE: Endocrine cell lines originated from mammalian hypothalamus and pancreatic islet, applicable in expression cloning systems of bioactive peptide precursor genes, and in screening G protein-coupled receptor ligands.
DERWENT CLASS: B04 D16
INVENTOR(S): KISHIMOTO, K; KUNITOMO, H; MIURA, K; NISHI, T; OBINATA, M; SAEKI, S; SASAKI, K; YOSHIZAWA, M
PATENT ASSIGNEE(S): (KYOW) KYOWA HAKKO KOGYO KK
COUNTRY COUNT: 103
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2003087366	A1	20031023	(200377)*	JA	316
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW					
AU 2003235193	A1	20031027	(200436)		
EP 1498483	A1	20050119	(200506)	EN	
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR					
JP 2003584307	X	20050818	(200554)		235

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2003087366	A1	WO 2003-JP4840	20030416
AU 2003235193	A1	AU 2003-235193	20030416
EP 1498483	A1	EP 2003-719119	20030416
		WO 2003-JP4840	20030416
JP 2003584307	X	JP 2003-584307	20030416
		WO 2003-JP4840	20030416

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2003235193	A1	Based on	WO 2003087366
EP 1498483	A1	Based on	WO 2003087366
JP 2003584307	X	Based on	WO 2003087366

PRIORITY APPLN. INFO: JP 2002-113030 20020416

L12 ANSWER 32 OF 59 CAPLUS COPYRIGHT 2006 ACS on STN
TI Method for clostripain-specific cleavage and amidation of universal recombinant bioactive peptides
SO PCT Int. Appl., 123 pp.
CODEN: PIXXD2
IN Wagner, Fred W.; Luan, Peng; Xia, Yuannan; Strydom, Daniel; Merrifield, Edwin H.; Bossard, Mary J.; Holmquist, Barton; Seo, Jin Seog
AB The invention provides methods for making peptides from a polypeptide containing at least one copy of the peptide using clostripain to excise the peptide from the polypeptide. The methods enable the use of a

single, highly efficient enzymic cleavage to produce any desired peptide sequence. The methods enable the use of a single, highly efficient enzymic cleavage to produce any desired peptide sequence. These and other needs are achieved by a site specific clostripain cleavage. Methods is exemplified by recombinant preparation of a single or multicopy polypeptide having or containing a peptide sequence of the Formula GLP-2-(1-33), GLP-2-(1-33,A2G), GLP-1-(7-36) GLP-1-(1-37) and mutations, permutations and conservative substitutions thereof. These purified recombinant GLP-2 proteins are subjected to clostripain specific cleavage, transpeptidation and C-terminal amidation to release of a single copy of the desired peptide. The precise release of desired GLP-2 peptides is accomplished through use of Arg-ending linker peptide in the recombinant GLP-2 polypeptide to ensure selective clostripain cleavage. Also disclosed are linker peptides with various formulas and several inclusion body leader partner peptides for isolation enhancement of recombinant proteins.

ACCESSION NUMBER: 2003:951049 CAPLUS
DOCUMENT NUMBER: 140:13435
TITLE: Method for clostripain-specific cleavage and amidation of universal recombinant bioactive peptides
INVENTOR(S): Wagner, Fred W.; Luan, Peng; Xia, Yuannan; Strydom, Daniel; Merrifield, Edwin H.; Bossard, Mary J.; Holmquist, Barton; Seo, Jin Seog
PATENT ASSIGNEE(S): Restoragen Inc., USA
SOURCE: PCT Int. Appl., 123 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003099848	A2	20031204	WO 2003-US16470	20030523
WO 2003099848	A3	20040916		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2485695	AA	20031204	CA 2003-2485695	20030523
AU 2003239865	A1	20031212	AU 2003-239865	20030523
EP 1513945	A2	20050316	EP 2003-734173	20030523
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2006008870	A1	20060112	US 2004-997074	20041124
PRIORITY APPLN. INFO.:			US 2002-383380P P	20020524
			WO 2003-US16470 W	20030523

L12 ANSWER 33 OF 59 CAPLUS COPYRIGHT 2006 ACS on STN
TI Method for enzymatic cleavage and amidation of recombinant GLP-1 (7-36) peptides
SO PCT Int. Appl., 103 pp.
CODEN: PIXXD2
IN Wagner, Fred W.; Luan, Peng; Xia, Yuannan; Bossard, Mary J.; Holmquist, Barton; Merrifield, Edwin H.; Strydom, Daniel
AB The invention provides methods for making peptides from a polypeptide containing at least one copy of the peptide using clostripain to

excise the peptide from the polypeptide. The methods enable the use of a single, highly efficient enzymic cleavage to produce any desired peptide sequence. Methods for recombinant preparation of a single or multicopy polypeptide having or containing a peptide sequence of the Formula GLP -1(7-36), GLP-1-(7-36) amide, or GLP -1-(7-37) as well as conservative substitutions thereof are provided. These purified recombinant GLP-1 proteins are subjected to clostripain specific cleavage, transpeptidation and amidation for the release of a single copy of the desired peptide. The precise release of desired GLP-1 peptides is accomplished through use of Arg-ending linker peptide in the recombinant GLP-1 polypeptide to ensure selective clostripain cleavage. Also disclosed are various formulas for linker peptides and possible compns. of recombinant GLP-1 proteins.

ACCESSION NUMBER: 2003:951048 CAPLUS
DOCUMENT NUMBER: 140:13434
TITLE: Method for enzymatic cleavage and amidation of recombinant GLP-1 (7-36) peptides
INVENTOR(S): Wagner, Fred W.; Luan, Peng; Xia, Yuannan; Bossard, Mary J.; Holmquist, Barton; Merrifield, Edwin H.; Strydom, Daniel
PATENT ASSIGNEE(S): Restoragen Inc., USA
SOURCE: PCT Int. Appl., 103 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003099847	A2	20031204	WO 2003-US16469	20030523
WO 2003099847	A3	20041229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2485701	AA	20031204	CA 2003-2485701	20030523
AU 2003239863	A1	20031212	AU 2003-239863	20030523
EP 1551435	A2	20050713	EP 2003-734172	20030523
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2005260701	A1	20051124	US 2004-997061	20041124

PRIORITY APPLN. INFO.:
US 2002-383214P P 20020524
WO 2003-US16469 W 20030523

L12 ANSWER 34 OF 59 USPAT2 on STN
TI Human glucose-dependent insulin-secreting cell line
IN Perfetti, Riccardo, Los Angeles, CA, United States
AB Disclosed herein is a novel cell line of human pancreatic cells that secrete insulin in a glucose-dependent manner. The cell line comprises pancreatic cells, such as PANC-1 cells, which are transfected so as to express IDX-1 and cultured in GLP-1. The cell line may be used to investigate the function and development of pancreatic cells, as well as to test the efficacy of drugs that stimulate insulin secretion.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2003:165446 USPAT2
TITLE: Human glucose-dependent insulin-secreting cell line
INVENTOR(S): Perfetti, Riccardo, Los Angeles, CA, United States
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, Los Angeles, CA, United States (U.S. corporation)

	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 6642003	B2	20031104	
APPLICATION INFO.:	US 2001-920868		20010802	(9)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Ketter, James
LEGAL REPRESENTATIVE: Pillsbury Winthrop LLP
NUMBER OF CLAIMS: 30
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 11 Drawing Figure(s); 12 Drawing Page(s)
LINE COUNT: 1253
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 35 OF 59 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
TI Structural basis of proline-specific exopeptidase activity as observed in human dipeptidyl peptidase-IV.
SO Structure, (1 Aug 2003) Vol. 11, No. 8, pp. 947-959. .
Refs: 72
ISSN: 0969-2126 CODEN: STRUE6
AU Thoma R.; Loffler B.; Stihle M.; Huber W.; Ruf A.; Hennig M.
AB Inhibition of dipeptidyl peptidase IV (DPP-IV), the main glucagon -like peptide 1 (GLP1)-degrading enzyme, has been proposed for the treatment of type II diabetes. We expressed and purified the ectodomain of human DPP-IV in Pichia pastoris and determined the X-ray structure at 2.1 A resolution. The enzyme consists of two domains, the catalytic domain, with an α/β hydrolase fold, and a β propeller domain with an 8-fold repeat of a four-strand β sheet motif. The β propeller domain contributes two important functions to the molecule that have not been reported for such structures, an extra β sheet motif that forms part of the dimerization interface and an additional short helix with a double Glu sequence motif. The Glu motif provides recognition and a binding site for the N terminus of the substrates, as revealed by the complex structure with diprotin A, a substrate with low turnover that is trapped in the tetrahedral intermediate of the reaction in the crystal.
ACCESSION NUMBER: 2003326643 EMBASE
TITLE: Structural basis of proline-specific exopeptidase activity as observed in human dipeptidyl peptidase-IV.
AUTHOR: Thoma R.; Loffler B.; Stihle M.; Huber W.; Ruf A.; Hennig M.
CORPORATE SOURCE: M. Hennig, F. Hoffmann-La Roche AG, Pharma Research Discovery, 4070 Basel, Switzerland. michael.hennig@roche.com
SOURCE: Structure, (1 Aug 2003) Vol. 11, No. 8, pp. 947-959. .
Refs: 72
ISSN: 0969-2126 CODEN: STRUE6
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 28 Aug 2003
Last Updated on STN: 28 Aug 2003

L12 ANSWER 36 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN

TI METHODS FOR PRODUCTION OF RECOMBINANT POLYPEPTIDES; GENERATING PREFERENTIAL POLYPEPTIDES; OBTAIN NUCLEOTIDE SEQUENCES, TRANSFORM VECTOR, EXPRESS VECTOR, RECOVER POLYPEPTIDE

INF Cottingham; Ian Robert, Edinburgh, GB
McKee; Colin Martin, Edinburgh, GB
Miller; Alan Robert, Edinburgh, GB

IN Cottingham Ian Robert (GB); McKee Colin Martin (GB); Miller Alan Robert (GB)

AB Methods for the production of peptides with authentic N-terminal are provided. DNA constructs are also described, which can be used in the production of transgenic animals, which produce the desired peptide in their milk.

CLMN 41 4 Figure(s).
FIG. 1: shows the complementary single stranded oligonucleotides used in the expression of various peptides as described in example 1;
FIG. 2: shows the results of mass spectrum analysis of various recombinant peptides produced according to the methods of the invention;
FIG. 3: shows a mass spectrum analysis for a LHRH/LAMIN construct; and
FIG. 4: shows mass spectrum analysis for a peptide-thioester intermediate and the product of subsequent transfer to an acceptor, in this case ethylamine;

AN 10203072 IFIPAT;IFIUDB;IFICDB

TITLE: METHODS FOR PRODUCTION OF RECOMBINANT POLYPEPTIDES; GENERATING PREFERENTIAL POLYPEPTIDES; OBTAIN NUCLEOTIDE SEQUENCES, TRANSFORM VECTOR, EXPRESS VECTOR, RECOVER POLYPEPTIDE

INVENTOR(S): Cottingham; Ian Robert, Edinburgh, GB
McKee; Colin Martin, Edinburgh, GB
Miller; Alan Robert, Edinburgh, GB

PATENT ASSIGNEE(S): Unassigned
PATENT ASSIGNEE PROBABLE: PPL Therapeutics Ltd GB (Probable)
AGENT: CHRISTENSEN, O'CONNOR, JOHNSON, KINDNESS, PLLC, 1420 FIFTH AVENUE, SUITE 2800 SEATTLE, WA, 98101-2347, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2002146779	A1	20021010
APPLICATION INFORMATION:	US 2000-746945		20001221

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	WO 1999-GB1907	19990616	UNKNOWN

	NUMBER	DATE	
PRIORITY APPLN. INFO.:	GB 1998-139124	19980626	
	US 1998-98281P	19980828	(Provisional)
FAMILY INFORMATION:	US 2002146779	20021010	

DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 41 4 Figure(s).

DESCRIPTION OF FIGURES:

FIG. 1: shows the complementary single stranded oligonucleotides used in the expression of various peptides as described in example 1;
FIG. 2: shows the results of mass spectrum analysis of various recombinant peptides produced according to the methods of the invention;
FIG. 3: shows a mass spectrum analysis for a LHRH/LAMIN construct; and
FIG. 4: shows mass spectrum analysis for a peptide-thioester intermediate and the product of subsequent transfer to an acceptor, in this case ethylamine;

L12 ANSWER 37 OF 59 IFIPAT COPYRIGHT 2006 IFI on STN
TI CHLORELLA VIRUS PROMOTERS; OF GIVEN NUCLEOTIDE SEQUENCE, OPERABLY LINKED TO A DNA SEQUENCE ENCODING A STRUCTURAL GENE
INF Xia; Yuannan, Lincoln, NE, US
IN Xia Yuannan
AB The present invention provides novel promoter sequences obtained from Chlorella virus. The invention includes gene constructs comprising a promoter sequence of the invention operably linked to a DNA sequence encoding a structural gene. The invention also provides vectors and host cells for expressing product encoded by the structural gene of a gene construct of the invention amd cells transformed with the heterologous gene operably linked to the promoter.
CLMN 37 9 Figure(s).
FIG. 1 is a diagrammatic representation of the pKK232-8 plasmid map.
FIG. 2 is a diagrammatic representation of gene constructs using seven Chlorella virus promoters linked to the heterologous DNA sequence encoding the CAT protein.
FIG. 3 is a comparison of CAT activities in chloramphenicolresistant E. Coli transformed with the CAT gene operably linked to the promoter sequences cvp-10, cvp-13, cvp-15 and cvp-16.
FIG. 4 is a comparison of promoter activities of the Chlorella virus promoter cvp-13 and the tac promoter transformed into E. coli HB101 and grown in the presence of varying concentrations of chloramphenicol.
FIG. 5 is a diagrammatic representation of the pBN115-glp plasmid map.
FIG. 6 is an SDS-PAGE gel showing expression of GLP-1 from pBN 115-glp and pBN 115-glp/tac at various temperatures.
FIG. 7 is a photograph of an SDS polyacrylamide gel of proteins expressed from expression cassettes containing 3 copy GLP-I and YX16 promoter or tac promoter, induced and uninduced, soluble and insoluble protein, at 27 degrees C. and 37 degrees C.
FIG. 8 a photograph of an SDS polyacrylamide gel of proteins expressed from expression cassettes formed with 8 copy GLP-1 and the YX15, YX16, or tac promoter, induced and uninduced, soluble and insoluble protein, at 27 degrees C. and 37 degrees C.
FIG. 9 is a diagramatic representation of the plasmid map of pBN95lnk2(GLP(7-36)AFAM)8HAE(tac).

AN 10138110 IFIPAT;IFIUDB;IFICDB
TITLE: CHLORELLA VIRUS PROMOTERS; OF GIVEN NUCLEOTIDE SEQUENCE, OPERABLY LINKED TO A DNA SEQUENCE ENCODING A STRUCTURAL GENE
INVENTOR(S): Xia; Yuannan, Lincoln, NE, US
PATENT ASSIGNEE(S): BioNebraska, Inc.
AGENT: Beth A. Burrous FOLEY & LARDNER, Washington Harbor, 3000 K Street, N.W., Suite 500, Washington, DC, 20007-5109, US

	NUMBER	PK	DATE
PATENT INFORMATION:	US 2002081735	A1	20020627
APPLICATION INFORMATION:	US 2001-899999		20010709

	APPLN. NUMBER	DATE	GRANTED PATENT NO. OR STATUS
CONTINUATION OF:	WO 1998-US5655	19980321	UNKNOWN
CONTINUATION-IN-PART OF:	US 1997-821559	19970321	5846774
DIVISION OF:	US 1999-400541	19990921	6316224
FAMILY INFORMATION:	US 2002081735	20020627	
	US 5846774		
	US 6316224		

US 6395965 20020528
DOCUMENT TYPE: Utility
Patent Application - First Publication
FILE SEGMENT: CHEMICAL
APPLICATION

NUMBER OF CLAIMS: 37 9 Figure(s).
DESCRIPTION OF FIGURES:
FIG. 1 is a diagrammatic representation of the pKK232-8 plasmid map.
FIG. 2 is a diagrammatic representation of gene constructs using seven Chlorella virus promoters linked to the heterologous DNA sequence encoding the CAT protein.
FIG. 3 is a comparison of CAT activities in chloramphenicolresistant E. Coli transformed with the CAT gene operably linked to the promoter sequences cvp-10, cvp-13, cvp-15 and cvp-16.
FIG. 4 is a comparison of promoter activities of the Chlorella virus promoter cvp-13 and the tac promoter transformed into E. coli HB101 and grown in the presence of varying concentrations of chloramphenicol.
FIG. 5 is a diagrammatic representation of the pBN115-glp plasmid map.
FIG. 6 is an SDS-PAGE gel showing expression of GLP-***1*** from pBN 115-glp and pBN 115-glp/tac at various temperatures.
FIG. 7 is a photograph of an SDS polyacrylamide gel of proteins ***expressed*** from expression cassettes containing 3 copy GLP-I and YX16 promoter or tac promoter, induced and uninduced, soluble and insoluble protein, at 27 degrees C. and 37 degrees C.
FIG. 8 a photograph of an SDS polyacrylamide gel of proteins expressed from expression cassettes formed with 8 copy GLP-***1*** and the YX15, YX16, or tac promoter, induced and uninduced, soluble and insoluble protein, at 27 degrees C. and 37 degrees C.
FIG. 9 is a diagramatic representation of the plasmid map of pBN95lnk2(GLP(7-36)AFAM)8HAE(tac).

L12 ANSWER 38 OF 59 CAPLUS COPYRIGHT 2006 ACS on STN
TI Genetically engineered bacterium for producing recombinant glucagon like peptide GLP-1(7-36) and use
SO Faming Zhuanli Shenqing Gongkai Shuomingshu, 18 pp.
CODEN: CNXXEV
IN Sun, Yukun; Wu, Dengxi; Wu, Aizhen; Zhu, Zhiyong; Yu, Gang; Zhou, Jiaxiang; Zhao, Shaoling
AB The invention provides a genetically engineered E.coli carrying the plasmid containing 16 copies of gene encoding 1-32 of glucagon like peptide GLP-1(7-36) and the promoter, which may be used to secret GLP-1(7-36). The invention also relates to the prodn. of GLP-1 (7-36) by fermentation of the genetically engineered E.coli.
ACCESSION NUMBER: 2003:519630 CAPLUS
DOCUMENT NUMBER: 139:64356
TITLE: Genetically engineered bacterium for producing recombinant glucagon like peptide GLP-1(7-36) and use
INVENTOR(S): Sun, Yukun; Wu, Dengxi; Wu, Aizhen; Zhu, Zhiyong; Yu, Gang; Zhou, Jiaxiang; Zhao, Shaoling
PATENT ASSIGNEE(S): Shanghai Huayi Biological Technology Co., Ltd., Peop. Rep. China
SOURCE: Faming Zhuanli Shenqing Gongkai Shuomingshu, 18 pp.
CODEN: CNXXEV
DOCUMENT TYPE: Patent
LANGUAGE: Chinese
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CN 1363654	A	20020814	CN 2001-126278	20010719

CA 2454264	AA	20030227	CA 2002-2454264		20020717
WO 2003016349	A1	20030227	WO 2002-CN502		20020717
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM					
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG					
EP 1408050	A1	20040414	EP 2002-752955		20020717
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, SK					
BR 2002011435	A	20040713	BR 2002-11435		20020717
CN 1531551	A	20040922	CN 2002-814355		20020717
JP 2005515167	T2	20050526	JP 2003-521271		20020717
PRIORITY APPLN. INFO.:			CN 2001-126278	A	20010719
			WO 2002-CN502	W	20020717

L12 ANSWER 39 OF 59 USPAT2 on STN

TI In Vivo production and delivery of erythropoietin or insulinotropin for gene therapy

IN Selden, Richard F., Wellesley, MA, United States
Treco, Douglas, Arlington, MA, United States
Heartlein, Michael W., Boxborough, MA, United States

AB The invention provides primary and secondary cells that are transfected with a nucleic acid molecule that encodes erythropoietin, clonal or heterogenous strains of such cells, and methods of producing these cell strains.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER: 2002:280161 USPAT2

TITLE: In Vivo production and delivery of erythropoietin or insulinotropin for gene therapy

INVENTOR(S): Selden, Richard F., Wellesley, MA, United States
Treco, Douglas, Arlington, MA, United States
Heartlein, Michael W., Boxborough, MA, United States

PATENT ASSIGNEE(S): Transkaryotic Therapies, Inc., Cambridge, MA, United States (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6846676	B2	20050125
APPLICATION INFO.:	US 1999-328130		19990608 (9)

RELATED APPLN. INFO.: Continuation of Ser. No. US 1994-334455, filed on 4 Nov 1994, now patented, Pat. No. US 5994127 Continuation of Ser. No. US 1992-911533, filed on 10 Jul 1992, now abandoned Continuation-in-part of Ser. No. US 1991-787840, filed on 5 Nov 1991, now abandoned Continuation-in-part of Ser. No. US 1991-789188, filed on 5 Nov 1991, now abandoned

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Ketter, James
ASSISTANT EXAMINER: Katcheves, Konstantina
LEGAL REPRESENTATIVE: Clark & Elbing LLP
NUMBER OF CLAIMS: 70
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Figure(s); 7 Drawing Page(s)
LINE COUNT: 2077

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 40 OF 59 USPAT2 on STN
TI Immunologically privileged cells and uses thereof
IN Lipes, Myra A., Brookline, MA, UNITED STATES
Chen, Qian, Lowell, MA, UNITED STATES
AB The invention is directed to immunologically privileged cells, e.g., autologous, allogeneic, and xenogeneic intermediate lobe pituitary cells, for delivering polypeptides, e.g., insulin, to a subject, and to methods of using the same.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:193032 USPAT2		
TITLE:	Immunologically privileged cells and uses thereof		
INVENTOR(S):	Lipes, Myra A., Brookline, MA, UNITED STATES Chen, Qian, Lowell, MA, UNITED STATES		
PATENT ASSIGNEE(S):	Joslin Diabetes Center, Inc., Boston, MA, UNITED STATES (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 7033585	B2	20060425
APPLICATION INFO.:	US 2001-770601		20010126 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1998-127296, filed on 30 Jul 1998, ABANDONED		
	NUMBER		DATE
PRIORITY INFORMATION:	US 1997-54730P		19970805 (60)
DOCUMENT TYPE:	Utility		
FILE SEGMENT:	GRANTED		
PRIMARY EXAMINER:	Falk, Anne-Marie		
LEGAL REPRESENTATIVE:	Fish & Richardson P.C.		
NUMBER OF CLAIMS:	10		
EXEMPLARY CLAIM:	1		
NUMBER OF DRAWINGS:	7 Drawing Figure(s); 7 Drawing Page(s)		
LINE COUNT:	1988		

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 41 OF 59 USPAT2 on STN
TI Chlorella virus promoters
IN Xia, Yuannan, Lincoln, NE, UNITED STATES
AB The present invention provides novel promoter sequences obtained from Chlorella virus. The invention includes gene constructs comprising a promoter sequence of the invention operably linked to a DNA sequence encoding a structural gene. The invention also provides vectors and host cells for expressing product encoded by the structural gene of a gene construct of the invention amd cells transformed with the heterologous gene operably linked to the promoter.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

ACCESSION NUMBER:	2002:122825 USPAT2		
TITLE:	Chlorella virus promoters		
INVENTOR(S):	Xia, Yuannan, Lincoln, NE, UNITED STATES		
PATENT ASSIGNEE(S):	BioNebraska, Inc. (U.S. corporation)		
	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002081735	A1	20020627
APPLICATION INFO.:	US 2001-899999	A1	20010709 (9)
RELATED APPLN. INFO.:	Division of Ser. No. US 1999-400541, filed on 21 Sep 1999, GRANTED, Pat. No. US 6316224 Continuation of Ser. No. WO 1998-US5655, filed on 21 Mar 1998, UNKNOWN Continuation-in-part of Ser. No. US 1997-821559, filed on 21 Mar 1997, GRANTED, Pat. No. US 5846774		

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Beth A. Burrous, FOLEY & LARDNER, Washington Harbor, 3000 K Street, N.W., Suite 500, Washington, DC, 20007-5109
NUMBER OF CLAIMS: 37
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 9 Drawing Page(s)
LINE COUNT: 960
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 42 OF 59 USPAT2 on STN
TI Derivatives of GLP-1 analogs
IN Knudsen, Liselotte Bjerre, Valby, DENMARK
Huusfeldt, Per Olaf, K.o slashed.benhavn K, DENMARK
Nielsen, Per Franklin, V.ae butted.rl.o slashed.se, DENMARK
AB The present invention relates to a pharmaceutical composition comprising a GLP-1 derivative having a lipophilic substituent; and a surfactant.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
ACCESSION NUMBER: 2001:123563 USPAT2
TITLE: Derivatives of GLP-1 analogs
INVENTOR(S): Knudsen, Liselotte Bjerre, Valby, DENMARK
Huusfeldt, Per Olaf, K.o slashed.benhavn K, DENMARK
Nielsen, Per Franklin, V.ae butted.rl.o slashed.se, DENMARK
PATENT ASSIGNEE(S): Novo Nordisk A/S, Bagsvaerd, DENMARK (non-U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 6458924	B2	20021001
APPLICATION INFO.:	US 1999-398111		19990916 (9)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1999-265141, filed on 8 Mar 1999, now patented, Pat. No. US 6384016 Continuation-in-part of Ser. No. US 1999-258750, filed on 26 Feb 1999, now patented, Pat. No. US 6268343 Continuation-in-part of Ser. No. US 1998-38432, filed on 11 Mar 1998, now abandoned Continuation-in-part of Ser. No. US 918810, now abandoned

	NUMBER	DATE
PRIORITY INFORMATION:	DK 1996-931	19960830
	DK 1996-1259	19961108
	DK 1996-1470	19961220
	DK 1998-263	19980227
	DK 1998-264	19980227
	DK 1998-268	19980227
	DK 1998-272	19980227
	DK 1998-274	19980227
	EP 1998-610006	19980313
	DK 1998-508	19980408
	DK 1998-509	19980408
	DK 1998-507	19980408
	US 1997-35904P	19970124 (60)
	US 1997-36226P	19970125 (60)
	US 1997-36255P	19970124 (60)
	US 1998-78422P	19980318 (60)
	US 1998-82478P	19980421 (60)
	US 1998-82479P	19980421 (60)
	US 1998-82480P	19980421 (60)
	US 1998-82802P	19980423 (60)
	US 1998-84357P	19980505 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: GRANTED
PRIMARY EXAMINER: Low, Christopher S. F.
ASSISTANT EXAMINER: Lukton, David
LEGAL REPRESENTATIVE: Green, Esq., Reza, Bork, Esq., Richard
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 1 Drawing Figure(s); 1 Drawing Page(s)
LINE COUNT: 15067
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L12 ANSWER 43 OF 59 WPIDS COPYRIGHT 2006 THE THOMSON CORP on STN
TI Novel methods for production of peptides with authentic amino-termini, and peptide-acceptor conjugates.
IN COTTINGHAM, I R; MCKEE, C M; MILLAR, A R; MILLER, A R
AN 2000-170922 [15] WPIDS
AB WO 200000625 A UPAB: 20000323
NOVELTY - Production of a peptide (P) with an authentic amino terminal comprising expressing P as part of a fusion protein, wherein P incorporates a sequence extension at its N-terminus, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) production of a peptide-acceptor conjugate which comprising:
(a) expressing the peptide as part of a fusion protein;
(b) releasing the peptide from the fusion protein as a thioester intermediate; and
(c) reacting the intermediate with an acceptor moiety to form the conjugate;
(2) production of a peptide-acceptor conjugate which comprising:
(a) expressing the peptide as part of a fusion protein;
(b) forming a thioester intermediate directly with a thiol on the fusion partner;
(c) reacting the intermediate with an acceptor moiety to form the conjugate;
(3) production of a peptide (incorporating a secretory leader sequence at its amino terminus) with an authentic amino-terminal amino acid, comprising expressing the peptide as part of a fusion protein, where the fusion partner comprises a molecule capable of catalyzing transfer of the peptide to an acceptor;
(4) a DNA construct coding for the fusion protein of the invention, optionally in the form of a vector;
(5) a host cell transformed or transfected with the DNA construct of (4);
(6) a transgenic, non-human mammal (especially a pig, cow, sheep, goat or rabbit) which has the DNA construct of (4) integrated into its genome; and
(7) a peptide-acceptor conjugate produced by the methods of (1) or (2).
USE - The methods are used to make peptides with authentic amino terminal amino acids, and peptide-acceptor conjugates (claimed).
Dwg.0/4
ACCESSION NUMBER: 2000-170922 [15] WPIDS
DOC. NO. NON-CPI: N2000-127072
DOC. NO. CPI: C2000-053088
TITLE: Novel methods for production of peptides with authentic amino-termini, and peptide-acceptor conjugates.
DERWENT CLASS: B04 C06 D16 P14
INVENTOR(S): COTTINGHAM, I R; MCKEE, C M; MILLAR, A R; MILLER, A R
PATENT ASSIGNEE(S): (PPLT-N) PPL THERAPEUTICS SCOTLAND LTD; (COTT-I) COTTINGHAM I R; (MCKE-I) MCKEE C M; (MILL-I) MILLER A R
COUNTRY COUNT: 87
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

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      ------------------------------------------------
      WO 2000000625   A1 20000106 (200015)* EN   43
         RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL
             OA PT SD SE SL SZ UG ZW
          W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB
             GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU
             LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR
             TT UA UG US UZ VN YU ZA ZW
      AU 9943805      A  20000117 (200026)
      EP 1090132      A1 20010411 (200121)  EN
          R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
      US 2002146779   A1 20021010 (200269)

APPLICATION DETAILS:

      PATENT NO      KIND                  APPLICATION          DATE
      ------------------------------------------------------------------
      WO 2000000625   A1                  WO 1999-GB1907       19990616
      AU 9943805      A                    AU 1999-43805       19990616
      EP 1090132      A1                   EP 1999-926622      19990616
                                           WO 1999-GB1907      19990616
      US 2002146779   A1 Provisional       US 1998-98281P      19980828
                         Cont of           WO 1999-GB1907      19990616
                                           US 2000-746945      20001221

FILING DETAILS:

      PATENT NO       KIND                   PATENT NO
      ------------------------------------------------
      AU 9943805      A  Based on           WO 2000000625
      EP 1090132      A1 Based on           WO 2000000625

PRIORITY APPLN. INFO: US 1998-98281P       19980828; GB
                      1998-13912          19980626

L12  ANSWER 44 OF 59  WPIDS  COPYRIGHT 2006 THE THOMSON CORP on STN
TI   Production of glucagon-like peptide-1 (7-36) - using transformed bacteria
     containing 2 or more consecutive DNA sequences coding for GLP-1 (7-36).
IN   BJORN, S E; RASMUSSEN, J S; THIM, L
AN   1995-240671 [31]   WPIDS
AB   WO   9517510 A UPAB: 19950810
     Production of glucagon-like peptide 1
     (GLP-1) 7-36 or an analogue in a bacterium comprises:
     (a) inserting in a suitable expression vector an
     expression cassette comprising a DNA construct encoding a
     GLP-1 precursor containing 2 or more consecutive DNA
     sequences coding for GLP-1 (7-36) or an analogue, the
     DNA construct encoding the GLP-1 precursor being
     preceded by a promoter sequence controlling the expression of
     the  precursor, (b) transforming a bacterium with the expression
     vector obtd., (c) culturing the transformed bacterium to permit
     expression of the DNA construct encoding the GLP-
     1 precursor, (d) recovering the resulting GLP-1
     precursor and (e) processing the GLP-1 precursor to
     GLP-1 (7-36) or an analogue.
          USE - The GLP-1 (7-36), analogues and derivs.
     (especially GLP-1(7-37) and GLP-1
     (7-36)-NH2) can be used in the treatment of type 2 diabetes.
          ADVANTAGE - When more than one copy of the DNA sequence
     coding for GLP-1 (7-36) was inserted in tandem
     into an expression vector, the transformed bacterial
     cells produced precursor in high yields (approx. 100 mg/l). The
     yield was not related to the copy number of the coding sequence.
     No recovery of peptide was found when a single copy of the
```

coding sequence was used.
Dwg.0/1

ACCESSION NUMBER: 1995-240671 [31] WPIDS
DOC. NO. CPI: C1995-110391
TITLE: Production of glucagon-like peptide-1 (7-36) - using transformed bacteria containing 2 or more consecutive DNA sequences coding for GLP-1 (7-36).
DERWENT CLASS: B04 D16
INVENTOR(S): BJORN, S E; RASMUSSEN, J S; THIM, L
PATENT ASSIGNEE(S): (NOVO) NOVO-NORDISK AS
COUNTRY COUNT: 57
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9517510	A1	19950629	(199531)*	EN	27
RW: AT BE CH DE DK ES FR GB GR IE IT KE LU MC MW NL OA PT SD SE SZ					
W: AM AU BB BG BR BY CA CN CZ FI GE HU JP KG KP KR KZ LK LT LV MD MG MN NO NZ PL RO RU SI SK TJ TT UA US UZ VN					
AU 9512725	A	19950710	(199543)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 9517510	A1	WO 1994-DK487	19941222
AU 9512725	A	AU 1995-12725	19941222

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9512725	A	Based on	WO 9517510

PRIORITY APPLN. INFO: DK 1993-1440 19931223

L12 ANSWER 45 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Identification of genes subject to positive selection in uropathogenic strains of Escherichia coli: A comparative genomics approach
TITLE (TI): Direct Submission
JOURNAL (SO): Proc. Natl. Acad. Sci. U.S.A., 103 (15), 5977-5982 (2006)
JOURNAL (SO): Submitted (05-JAN-2006) Molecular Microbiology, Genetics, and Molecular Biology and Pharmacology, Washington University School of Medicine, 660 South Euclid Avenue, Saint Louis, MO 63110, USA
AUTHOR (AU): Chen,S.L.; Hung,C.-S.; Xu,J.; Reigstad,C.S.; Magrini,V.; Sabo,A.; Blasiar,D.; Bieri,T.; Meyer,R.R.; Ozersky,P.; Armstrong,J.R.; Fulton,R.S.; Latreille,J.P.; Spieth,J.; Hooton,T.M.; Mardis,E.R.; Hultgren,S.J.; Gordon,J.I.
AUTHOR (AU): Chen,S.L.; Hung,C.-S.; Xu,J.; Reigstad,C.S.; Magrini,V.; Sabo,A.; Blasiar,D.; Bieri,T.; Meyer,R.R.; Ozersky,P.; Armstrong,J.R.; Fulton,R.S.; Latreille,J.P.; Spieth,J.; Hooton,T.M.; Mardis,E.R.; Hultgren,S.J.; Gordon,J.I.

L12 ANSWER 46 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Genome dynamics and diversity of Shigella species, the etiologic agents of bacillary dysentery
TITLE (TI): Direct Submission

JOURNAL (SO): Nucleic Acids Res., 33 (19), 6445-6458 (2005)
JOURNAL (SO): Submitted (29-OCT-2004) State Key Laboratory for Moleclular Virology and Genetic Engineering, Microbial Genome Center of Chinese Ministry of Public Health, 6 Rongjing Eastern Street, BDA, Beijing 100176, P. R. China
AUTHOR (AU): Yang,F.; Yang,J.; Zhang,X.; Chen,L.; Jiang,Y.; Yan,Y.; Tang,X.; Wang,J.; Xiong,Z.; Dong,J.; Xue,Y.; Zhu,Y.; Xu,X.; Sun,L.; Chen,S.; Nie,H.; Peng,J.; Xu,J.; Wang,Y.; Yuan,Z.; Wen,Y.; Yao,Z.; Shen,Y.; Qiang,B.; Hou,Y.; Yu,J.; Jin,Q.
AUTHOR (AU): Jin,Q.; Yang,F.; Yang,J.; Jiang,Y.; Yan,Y.; Chen,L.; Zhang,X.; Peng,J.; Tang,X.; Xiong,Z.; Nie,H.; Dong,J.; Xue,Y.; Xu,X.; Zhu,Y.; Shen,Y.; Qiang,B.; Hou,Y.

L12 ANSWER 47 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Genome dynamics and diversity of Shigella species, the etiologic agents of bacillary dysentery
TITLE (TI): Direct Submission
JOURNAL (SO): Nucleic Acids Res., 33 (19), 6445-6458 (2005)
JOURNAL (SO): Submitted (29-OCT-2004) State Key Laboratory for Moleclular Virology and Genetic Engineering, Microbial Genome Center of Chinese Ministry of Public Health, 6 Rongjing Eastern Street, BDA, Beijing 100176, P. R. China
AUTHOR (AU): Yang,F.; Yang,J.; Zhang,X.; Chen,L.; Jiang,Y.; Yan,Y.; Tang,X.; Wang,J.; Xiong,Z.; Dong,J.; Xue,Y.; Zhu,Y.; Xu,X.; Sun,L.; Chen,S.; Nie,H.; Peng,J.; Xu,J.; Wang,Y.; Yuan,Z.; Wen,Y.; Yao,Z.; Shen,Y.; Qiang,B.; Hou,Y.; Yu,J.; Jin,Q.
AUTHOR (AU): Jin,Q.; Yang,F.; Yang,J.; Jiang,Y.; Yan,Y.; Chen,L.; Zhang,X.; Peng,J.; Tang,X.; Xiong,Z.; Nie,H.; Dong,J.; Xue,Y.; Xu,X.; Zhu,Y.; Shen,Y.; Qiang,B.; Hou,Y.

L12 ANSWER 48 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Genome dynamics and diversity of Shigella species, the etiologic agents of bacillary dysentery
TITLE (TI): Direct Submission
JOURNAL (SO): Nucleic Acids Res., 33 (19), 6445-6458 (2005)
JOURNAL (SO): Submitted (29-OCT-2004) State Key Laboratory for Moleclular Virology and Genetic Engineering, Microbial Genome Center of Chinese Ministry of Public Health, 6 Rongjing Eastern Street, BDA, Beijing 100176, P. R. China
AUTHOR (AU): Yang,F.; Yang,J.; Zhang,X.; Chen,L.; Jiang,Y.; Yan,Y.; Tang,X.; Wang,J.; Xiong,Z.; Dong,J.; Xue,Y.; Zhu,Y.; Xu,X.; Sun,L.; Chen,S.; Nie,H.; Peng,J.; Xu,J.; Wang,Y.; Yuan,Z.; Wen,Y.; Yao,Z.; Shen,Y.; Qiang,B.; Hou,Y.; Yu,J.; Jin,Q.
AUTHOR (AU): Jin,Q.; Yang,F.; Yang,J.; Jiang,Y.; Yan,Y.; Chen,L.; Zhang,X.; Peng,J.; Tang,X.; Xiong,Z.; Nie,H.; Dong,J.; Xue,Y.; Xu,X.; Zhu,Y.; Shen,Y.; Qiang,B.; Hou,Y.

L12 ANSWER 49 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): The genome sequence of Salmonella enterica serovar Choleraesuis, a highly invasive and resistant zoonotic pathogen
TITLE (TI): Direct Submission
JOURNAL (SO): Nucleic Acids Res., 33 (5), 1690-1698 (2005)
JOURNAL (SO): Submitted (03-SEP-2004) Chang Gung Genomic Medical Center, No. 5, Fu-Shing St., Kweishan, Taoyuan 333,

Taiwan
AUTHOR (AU): Chiu,C.H.; Tang,P.; Chu,C.; Hu,S.; Bao,Q.; Yu,J.; Chou,Y.Y.; Wang,H.S.; Lee,Y.S.
AUTHOR (AU): Chiu,C.-H.; Tang,P.; Chu,C.; Bao,Q.; Hu,S.; Yu,J.; Chou,Y.-Y.; Wang,H.-S.; Lee,Y.-S.

L12 ANSWER 50 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Complete Genome Sequence and Comparative Genomics of Shigella flexneri Serotype 2a Strain 2457T
TITLE (TI): Direct Submission
JOURNAL (SO): Infect. Immun., 71 (5), 2775-2786 (2003)
JOURNAL (SO): Submitted (13-JUN-2002) Genetics Laboratory, University of Wisconsin - Madison, 445 Henry Mall, Madison, WI 53706, USA
AUTHOR (AU): Wei,J.; Goldberg,M.B.; Burland,V.; Venkatesan,M.M.; Deng,W.; Fournier,G.; Mayhew,G.F.; Plunkett,G. III; Rose,D.J.; Darling,A.; Mau,B.; Perna,N.T.; Payne,S.M.; Runyen-Janecky,L.J.; Zhou,S.; Schwartz,D.C.; Blattner,F.R.
AUTHOR (AU): Wei,J.; Goldberg,M.B.; Burland,V.; Venkatesan,M.M.; Deng,W.; Fournier,G.; Mayhew,G.F.; Plunkett,G. III; Rose,D.J.; Darling,A.; Mau,B.; Perna,N.T.; Payne,S.M.; Runyen-Janecky,L.J.; Zhou,S.; Schwartz,D.C.; Blattner,F.R.

L12 ANSWER 51 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Genome sequence of Shigella flexneri 2a: insights into pathogenicity through comparison with genomes of Escherichia coli K12 and O157
TITLE (TI): Direct Submission
TITLE (TI): Direct Submission
JOURNAL (SO): Nucleic Acids Res., 30 (20), 4432-4441 (2002)
JOURNAL (SO): Submitted (21-MAY-2001) State Key Laboratory for Moleclular Virology and Genetic Engineering, Microbial Genome Center of Chinese Ministry of Public Health, 6 Rongjing Eastern Street, BDA, Beijing 100176, P.R.China
JOURNAL (SO): Submitted (06-DEC-2004) State Key Laboratory for Moleclular Virology and Genetic Engineering, Microbial Genome Center of Chinese Ministry of Public Health, 6 Rongjing Eastern Street, BDA, Beijing 100176, P.R.China
AUTHOR (AU): Jin,Q.; Yuan,Z.; Xu,J.; Wang,Y.; Shen,Y.; Lu,W.; Wang,J.; Liu,H.; Yang,J.; Yang,F.; Zhang,X.; Zhang,J.; Yang,G.; Wu,H.; Qu,D.; Dong,J.; Sun,L.; Xue,Y.; Zhao,A.; Gao,Y.; Zhu,J.; Kan,B.; Ding,K.; Chen,S.; Cheng,H.; Yao,Z.; He,B.; Chen,R.; Ma,D.; Qiang,B.; Wen,Y.; Hou,Y.; Yu,J.
AUTHOR (AU): Jin,Q.; Shen,Y.; Wang,J.H.; Liu,H.; Yang,J.; Yang,F.; Zhang,X.B.; Zhang,J.Y.; Yang,G.W.; Wu,H.T.; Dong,J.; Sun,L.L.; Xue,Y.; Zhao,A.L.; Gao,Y.S.; Zhu,J.P.; Chen,S.X.; Yao,Z.J.; Wang,Y.; Lu,W.C.; Qiang,B.Q.; Wen,Y.M.; Hou,Y.D.
AUTHOR (AU): Jin,Q.; Shen,Y.; Wang,J.H.; Liu,H.; Yang,J.; Yang,F.; Zhang,X.B.; Zhang,J.Y.; Yang,G.W.; Wu,H.T.; Dong,J.; Sun,L.L.; Xue,Y.; Zhao,A.L.; Gao,Y.S.; Zhu,J.P.; Chen,S.X.; Yao,Z.J.; Wang,Y.; Lu,W.C.; Qiang,B.Q.; Wen,Y.M.; Hou,Y.D.

L12 ANSWER 52 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Genome Sequence of Yersinia pestis KIM
TITLE (TI): Direct Submission
JOURNAL (SO): J. Bacteriol., 184 (16), 4601-4611 (2002)

JOURNAL (SO): Submitted (21-FEB-2002) Genetics, University of Wisconsin, 445 Henry Mall, Madison, WI 53706, USA
AUTHOR (AU): Deng,W.; Burland,V.; Plunkett,G. III; Boutin,A.; Mayhew,G.F.; Liss,P.; Perna,N.T.; Rose,D.J.; Mau,B.; Zhou,S.; Schwartz,D.C.; Fetherston,J.D.; Lindler,L.E.; Brubaker,R.R.; Plana,G.V.; Straley,S.C.; McDonough,K.A.; Nilles,M.L.; Matson,J.S.; Blattner,F.R.; Perry,R.D.
AUTHOR (AU): Deng,W.; Burland,V.; Plunkett,G. III; Boutin,A.; Mayhew,G.F.; Liss,P.; Perna,N.T.; Rose,D.J.; Mau,B.; Zhou,S.; Schwartz,D.C.; Fetherston,J.D.; Lindler,L.E.; Brubaker,R.R.; Plana,G.V.; Straley,S.C.; McDonough,K.A.; Nilles,M.L.; Matson,J.S.; Blattner,F.R.; Perry,R.D.

L12 ANSWER 53 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Complete nucleotide sequence of the prophage VT2-Sakai carrying the verotoxin 2 genes of the enterohemorrhagic Escherichia coli O157:H7 derived from the Sakai outbreak
TITLE (TI): Comparative analysis of the whole set of rRNA operons between an enterohemorrhagic Escherichia coli O157:H7 Sakai strain and an Escherichia coli K-12 strain MG1655
TITLE (TI): Complete nucleotide sequence of the prophage VT1-Sakai carrying the Shiga toxin 1 genes of the enterohemorrhagic Escherichia coli O157:H7 strain derived from the Sakai outbreak
TITLE (TI): Complete genome sequence of enterohemorrhagic Escherichia coli O157:H7 and genomic comparison with a laboratory strain K-12
TITLE (TI): Direct Submission
JOURNAL (SO): Genes Genet. Syst., 74 (5), 227-239 (1999)
JOURNAL (SO): Syst. Appl. Microbiol., 23 (3), 315-324 (2000)
JOURNAL (SO): Gene, 258 (1-2), 127-139 (2000)
JOURNAL (SO): DNA Res., 8 (1), 11-22 (2001)
JOURNAL (SO): Submitted (26-JUN-2000) Masahira Hattori, Kitasato Institute for Life Sciences, Kitasato University; Kitasato 1-15-1, Sagamihara, Kanagawa 228-8555, Japan (E-mail:hattori@genome.ls.kitasato-u.ac.jp, URL:http://genome.ls.kitasato-u.ac.jp/, Tel:81-42-778-8194, Fax:81-42-778-8193)
AUTHOR (AU): Makino,K.; Yokoyama,K.; Kubota,Y.; Yutsudo,C.H.; Kimura,S.; Kurokawa,K.; Ishii,K.; Hattori,M.; Tatsuno,I.; Abe,H.; Iida,T.; Yamamoto,K.; Onishi,M.; Hayashi,T.; Yasunaga,T.; Honda,T.; Sasakawa,C.; Shinagawa,H.
AUTHOR (AU): Ohnishi,M.; Murata,T.; Nakayama,K.; Kuhara,S.; Hattori,M.; Kurokawa,K.; Yasunaga,T.; Yokoyama,K.; Makino,K.; Shinagawa,H.; Hayashi,T.
AUTHOR (AU): Yokoyama,K.; Makino,K.; Kubota,Y.; Watanabe,M.; Kimura,S.; Yutsudo,C.H.; Kurokawa,K.; Ishii,K.; Hattori,M.; Tatsuno,I.; Abe,H.; Yoh,M.; Iida,T.; Ohnishi,M.; Hayashi,T.; Yasunaga,T.; Honda,T.; Sasakawa,C.; Shinagawa,H.
AUTHOR (AU): Hayashi,T.; Makino,K.; Ohnishi,M.; Kurokawa,K.; Ishii,K.; Yokoyama,K.; Han,C.G.; Ohtsubo,E.; Nakayama,K.; Murata,T.; Tanaka,M.; Tobe,T.; Iida,T.; Takami,H.; Honda,T.; Sasakawa,C.; Ogasawara,N.; Yasunaga,T.; Kuhara,S.; Shiba,T.; Hattori,M.; Shinagawa,H.
AUTHOR (AU): Hattori,M.; Ishii,K.; Shiba,T.

L12 ANSWER 54 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): Genome sequence of enterohaemorrhagic Escherichia coli O157:H7
TITLE (TI): Direct Submission
JOURNAL (SO): Nature, 409 (6819), 529-533 (2001)
JOURNAL (SO): Submitted (22-OCT-2000) Laboratory of Genetics, University of Wisconsin, 445 Henry Mall, Madison, WI 53706, USA
AUTHOR (AU): Perna,N.T.; Plunkett,G. III; Burland,V.; Mau,B.; Glasner,J.D.; Rose,D.J.; Mayhew,G.F.; Evans,P.S.; Gregor,J.; Kirkpatrick,H.A.; Posfai,G.; Hackett,J.; Klink,S.; Boutin,A.; Shao,Y.; Miller,L.; Grotbeck,E.J.; Davis,N.W.; Lim,A.; Dimalanta,E.; Potamousis,K.; Apodaca,J.; Anantharaman,T.S.; Lin,J.; Yen,G.; Schwartz,D.C.; Welch,R.A.; Blattner,F.R.
AUTHOR (AU): Perna,N.T.; Plunkett,G. III; Burland,V.; Mau,B.; Glasner,J.D.; Rose,D.J.; Mayhew,G.F.; Evans,P.S.; Gregor,J.; Kirkpatrick,H.A.; Posfai,G.; Hackett,J.; Klink,S.; Boutin,A.; Shao,Y.; Miller,L.; Grotbeck,E.J.; Davis,N.W.; Lim,A.; Dimalanta,E.; Potamousis,K.; Apodaca,J.; Anantharaman,T.S.; Lin,J.; Yen,G.; Schwartz,D.C.; Welch,R.A.; Blattner,F.R.

L12 ANSWER 55 OF 59 GENBANK® COPYRIGHT 2006 on STN

TITLE (TI): The complete genome sequence of Escherichia coli K-12
TITLE (TI): Escherichia coli K-12: a cooperatively developed annotation snapshot--2005
TITLE (TI): Workshop on Annotation of Escherichia coli K-12
TITLE (TI): ASAP: Escherichia coli K-12 strain MG1655 version m56
TITLE (TI): A more accurate sequence comparison between genomes of Escherichia coli K12 W3110 and MG1655 strains
TITLE (TI): Escherichia coli K-12 MG1655 yqiK-rfaE intergenic region, genomic sequence correction
TITLE (TI): A manual approach to accurate translation start site annotation: an E. coli K-12 case study
TITLE (TI): Direct Submission
TITLE (TI): Direct Submission
TITLE (TI): Direct Submission
TITLE (TI): Direct Submission
TITLE (TI): Direct Submission
JOURNAL (SO): Science, 277 (5331), 1453-1474 (1997)
JOURNAL (SO): (er) Nucleic Acids Res., 34 (1), 1-9 (2006)
JOURNAL (SO): Unpublished
JOURNAL (SO): Unpublished
JOURNAL (SO): Unpublished
JOURNAL (SO): Unpublished
JOURNAL (SO): Unpublished
JOURNAL (SO): Submitted (16-JAN-1997) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
JOURNAL (SO): Submitted (02-SEP-1997) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
JOURNAL (SO): Submitted (13-OCT-1998) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
JOURNAL (SO): Submitted (10-JUN-2004) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
JOURNAL (SO): Submitted (07-FEB-2006) Laboratory of Genetics, University of Wisconsin, 425G Henry Mall, Madison, WI 53706-1580, USA
AUTHOR (AU): Blattner,F.R.; Plunkett,G.; Bloch,C.A.; Perna,N.T.;

Burland,V.; Riley,M.; Collado-Vides,J.; Glasner,J.D.; Rode,C.K.; Mayhew,G.F.; Gregor,J.; Davis,N.W.; Kirkpatrick,H.A.; Goeden,M.A.; Rose,D.J.; Mau,B.; Shao,Y.

AUTHOR (AU): Riley,M.; Abe,T.; Arnaud,M.B.; Berlyn,M.K.; Blattner,F.R.; Chaudhuri,R.R.; Glasner,J.D.; Horiuchi,T.; Keseler,I.M.; Kosuge,T.; Mori,H.; Perna,N.T.; Plunkett,G. III; Rudd,K.E.; Serres,M.H.; Thomas,G.H.; Thomson,N.R.; Wishart,D.; Wanner,B.L.

AUTHOR (AU): Arnaud,M.; Berlyn,M.K.B.; Blattner,F.R.; Galperin,M.Y.; Glasner,J.D.; Horiuchi,T.; Kosuge,T.; Mori,H.; Perna,N.T.; Plunkett,G. III; Riley,M.; Rudd,K.E.; Serres,M.H.; Thomas,G.H.; Wanner,B.L.

AUTHOR (AU): Glasner,J.D.; Perna,N.T.; Plunkett,G. III; Anderson,B.D.; Bockhorst,J.; Hu,J.C.; Riley,M.; Rudd,K.E.; Serres,M.H.

AUTHOR (AU): Hayashi,K.; Morooka,N.; Mori,H.; Horiuchi,T.

AUTHOR (AU): Perna,N.T.

AUTHOR (AU): Rudd,K.E.

AUTHOR (AU): Blattner,F.R.; Plunkett,G. III.

AUTHOR (AU): Blattner,F.R.; Plunkett,G. III.

AUTHOR (AU): Plunkett,G. III.

AUTHOR (AU): Plunkett,G. III.

AUTHOR (AU): Plunkett,G. III.

L12 ANSWER 56 OF 59 INVESTEXT COPYRIGHT 2006 TFS on STN

TI SANOFI AVENTIS
AU MANN, P., ET AL
Accession No.: 2008:786385 INVESTEXT(tm) REPORT NUMBER:11083549
Page No.: PAGE 23 OF 29
Document No.: 11083549
Title: SANOFI AVENTIS
Author: MANN, P., ET AL
Corp. Source: DEUTSCHE BANK SECURITIES LTD.; UNITED KINGDOM/GREAT BRITAIN/BRITISH ISLES
Region: WESTERN EUROPE REGION; EUROPE
Publication Date: 28 Mar 2006
Report Type: COMPANY REPORT
File Segment: Text Page; COMPANY REPORT
Text Word Count: 628

L12 ANSWER 57 OF 59 INVESTEXT COPYRIGHT 2006 TFS on STN

TI Drug Delivery Industry
AU Sanderson, I.C., et al
Accession No.: 1999:147071 INVESTEXT(tm) REPORT NUMBER:2761754
Page No.: PAGE 17 OF 204
Document No.: 2761754
Title: Drug Delivery Industry
Author: Sanderson, I.C., et al
Corp. Source: SG COWEN SECURITIES CORPORATION; MASSACHUSETTS (COMMONWEALTH OF)
Region: NEW ENGLAND/NORTHEAST REGION; UNITED STATES OF AMERICA; NORTH AMERICA
Corp. So. Type: Financial center investment bank-broker
Publication Date: 11 Sep 1998
Report Type: INDUSTRY REPORT
File Segment: Text Page; INDUSTRY REPORT
Text Word Count: 436

L12 ANSWER 58 OF 59 INVESTEXT COPYRIGHT 2006 TFS on STN

TI Drug Delivery Industry

AU Sanderson, I.C., et al
Accession No.: 1998:518100 INVESTEXT(tm) REPORT NUMBER:2647852
Page No.: PAGE 17 OF 198
Document No.: 2647852
Title: Drug Delivery Industry
Author: Sanderson, I.C., et al
Corp. Source: COWEN & COMPANY; MASSACHUSETTS (COMMONWEALTH OF)
Region: NEW ENGLAND/NORTHEAST REGION; UNITED STATES OF AMERICA; NORTH AMERICA
Corp. So. Type: Financial center investment bank-broker
Publication Date: 2 Mar 1998
Report Type: INDUSTRY REPORT
File Segment: Text Page; INDUSTRY REPORT
Text Word Count: 392

L12 ANSWER 59 OF 59 DGENE COPYRIGHT 2006 The Thomson Corp on STN
TI Biocompatible composition, useful to treat diabetes, obesity, Alzheimer's and cardiovascular disease, comprises a carrier with a metal binding domain, a metal ion and glucagon-like peptide-1 with a metal binding domain.
IN Bolotin E M
AN AEE19684 peptide DGENE
AB The present sequence is that of the chicken lactate dehydrogenase HAT histidine tag, used in the present invention to purify a Green Fluorescent Protein (GFP) variant of a novel biocompatible composition. Human glucagon-like peptide 1 (GLP-1) is part of the biocompatible composition, comprising a carrier with a metal binding domain (MBD), a metal ion chelated to metal binding domains of both the carrier and GLP-1 (naturally occurring within the peptide chain or otherwise), where after administration of the composition, GLP-1 is released from the carrier. The carrier comprises a poly amino acid, preferably poly-L-lysine (PL), poly(ethyleneglycol) and a protective sidechain preferably methoxy poly(ethyleneglycol) (MPEG). The metal binding domain comprises a nitrogen-containing poly carboxylic acid, preferably nitrilotriacetic acid (NTA). The metal ion is a transition metal ion, preferably Zn 2+ or Ni 2+. The carrier is a polymer, preferably 10000-250000 daltons in size, such as a micelle, reverse micelle, liposome, emulsion, hydrogel, microparticle, nanoparticle, microsphere or solid surface. A humanized GFP isoform cDNA was excised from BlueScriptGFP vector using compatible restriction sites. GFP fragment was subcloned into pHAT10 vector to afford in-frame expression with His-tag (HAT) from chicken lactate dehydrogenase containing six histidines. Ligation reactions were used for Escherichia coli transformation, and subsequently histidine-tagged GFP was expressed and purified. Complex formation between Ni 2+ or Zn 2+ salts of NTA-conjugated MPEG-PL copolymer and histidine-tagged GFP was achieved and shown to be highly specific in the presence or absence of plasma. These complexes were injected into mice and the Ni-complex was shown to be present in significantly higher levels in vivo for longer compared to the non-complexed histidine-tagged GFP control. GLP-1 is a potent intestinal hormone that increases insulin secretion from pancreatic beta cells and is thought to also strongly enhance the neogenesis of beta cells and prevent their apoptosis. Thus GLP-1 is a potential therapeutic agent for both insulin dependent and non-insulin dependent diabetes. GLP-1 half-life is decreased to 2-6 minutes in the blood stream as a result of the N-terminal cleavage at the Ala2 position by dipeptidyl peptidase IV (DPP-IV), seriously limiting its therapeutic potential. The present invention overcomes these problems by protecting the natural form of GLP-1. The composition of the invention is useful to treat obesity, Alzheimer's disease and cardiovascular disease as well as diabetes.
ACCESSION NUMBER: AEE19684 peptide DGENE

TITLE: Biocompatible composition, useful to treat diabetes, obesity, Alzheimer's and cardiovascular disease, comprises a carrier with a metal binding domain, a metal ion and glucagon-like peptide-1 with a metal binding domain.
INVENTOR: Bolotin E M
PATENT ASSIGNEE: (BOLO-I)BOLOTIN E M.
PATENT INFO: US 2005260259 A1 20051124 38
APPLICATION INFO: US 2005-112879 20050422
PRIORITY INFO: US 2004-564710P 20040423
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: 2006-036258 [04]
DESCRIPTION: Chicken lactate dehydrogenase HAT histidine tag.

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